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Soft tissue changes following extraction vs. nonextraction orthodontic fixed appliance treatment: a systematic review and meta-analysis

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Abstract: The aim of this systematic review was to assess the effect of systematic extraction protocols during orthodontic fixed appliance treatment on the soft tissue profile of human patients. Nine databases were searched until December 2016 for controlled clinical studies including premolar extraction or nonextraction treatment. After elimination of duplicate studies, data extraction, and risk-of-bias assessment according to the Cochrane guidelines, random-effects meta-analyses of mean differences (MD) or standardized mean differences (SMD) and their 95% CIs were performed, followed by subgroup, meta-regression, and sensitivity analyses. Extraction treatment was associated with increased lower lip retraction (24 studies; 1,456 patients; MD = 1.96 mm), upper lip retraction (21 studies; 1,149 patients; MD = 1.26 mm), nasolabial angle (21 studies; 1,089 patients; MD = 4.21°), soft-tissue profile convexity (six studies; 408 patients; MD = 1.24°), and profile pleasantness (three studies; 249 patients; SMD = 0.41). Patient age, extraction protocol, and amount of upper incisor retraction during treatment were significantly associated with the observed extraction effects, while the quality of evidence was very low in all cases due to risk of bias, baseline confounding, inconsistency, and imprecision. Although tooth extractions seem to affect patient profile, existing studies are heterogenous and no consistent predictions of profile response can be made.

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TITLE PAGE

Soft tissue changes in extraction versus non-extraction treatment with fixed orthodontic appliances: a systematic review and meta-analysis

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ABSTRACT

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Aim of this systematic review was to assess the effect of systematic extraction protocols during orthodontic fixed appliance treatment on the soft tissue profile of human patients. Nine databases were searched until December 2016 for controlled clinical studies including premolar extraction or non-extraction treatment. After elimination of duplicate studies, data extraction, and risk of bias assessment according to the Cochrane guidelines, random effects meta-analyses of Mean Differences (MD) or Standardized Mean Differences (SMD) and their 95% confidence intervals (CIs) were performed, followed by subgroup, meta-regression, and sensitivity analyses. Extraction treatment was associated with increased lower lip retraction (24 studies; 1,456 patients; MD=1.96 mm), upper lip retraction (21 studies; 1,149 patients; MD=1.26mm), nasolabial angle (21 studies; 1089 patients; MD=4.21º), soft tissue profile convexity (6 studies; 408 patients; MD=1.24 º), and profile pleasantness (3 studies; 249 patients; SMD=0.41). Patient age, extraction protocol, and amount of upper incisor retraction during treatment were significantly associated with the observed extraction effects, while the quality of evidence was very low in all cases due to risk of bias, baseline confounding, inconsistency and imprecision. Although tooth extractions seem to affect patient profile, existing studies are heterogenous and no consistent predictions of profile response can be made.

Key words: orthodontics; tooth extraction; face; clinical trial; review; meta-analysis

Introduction

Comprehensive orthodontic treatment with fixed appliances includes two vaguely mutually exclusive treatment modalities, extraction and non-extraction treatment. Extraction treatment is usually used to relieve moderate to severe crowding and/or alleviate dental or dentoalveolar protrusion. Non-extraction treatment is on the other hand preferred for cases of minor skeletal and moderate dental discrepancies. The choice between extraction and non-extraction is usually based on orthodontic training, treatment philosophy, or temporal trends (1, 2). At the same time, the choice to extract teeth might have substantial impact on various parameters like vertical dimension, treatment stability, or arch widths, as well as the perioral soft tissues and facial convexity (3–7).

Several published studies have reported on the comparison of various extraction treatment protocols with non-extraction treatment (4, 8–13) However, the critical appraisal of clinical evidence on the effects of extraction versus non-extraction treatment is closely associated to the implemented methodology. For one, patient randomization to such fundamentally different treatment protocols that are also associated with extraction of multiple healthy teeth might be challenging, and this might influence the study results (14). Therefore, in the absence of randomization, selection of cases to be compared in terms of adequate baseline matching is crucial in order to minimize baseline confounding, which might weaken the reliability of an investigation (15). Although several attempts have been made to contain such sources of bias in orthodontic literature of extraction treatment (3, 16, 17), most of the existing literature remains prone to bias.

A number of systematic reviews have attempted to assess the effect of orthodontic extraction treatment on the facial profile (18–20), but two of these did not perform quantitative synthesis (meta-analysis) (18–20). The third perfomed meta-analysis on panel assessments of esthetic preferences between Ex and Non-Ex patients,20 but included only a handful of studies and presented methodological issues (questionable basis for statistical model (21) or inadequate handling of heterogeneity (22)) that could affect their conclusions. Finally, none of the three reviews critically assesses the quality of meta-evidence and translated this into robust clinical recommendations using the GRADE approach (23).

Therefore, the aim of the present systematic review was to critically assess in an evidence-based manner clinical studies on the effect of orthodontic extraction on facial profile and to answer the research question: Is comprehensive treatment with tooth extractions associated with severe impediment of the facial profile of adolescent/adult patients compared to non-extraction treatment?

Material and methods

Protocol, eligibility criteria, and registration

The protocol for this review was made *a priori* based on the PRISMA-P statement (24), registered in PROSPERO (CRD42016049390), and all *post hoc* changes were appropriately noted. According to the Participants-Intervention-Comparison-Outcome-Study design (PICOS) schema, parallel randomized clinical trials and prospective non-randomized controlled cohort studies on human patients assessing the effect of any kind of systematic extraction protocol on the soft tissue profile were included. Cross-sectional studies, animal studies, non-clinical studies, and non-relevant studies were excluded (Table S1). This systematic review was conducted and reported according to the Cochrane Handbook (25) and PRISMA statement (26), respectively.

Information sources and literature search

A total of nine electronic databases were searched systematically by one author (SNP) without any limitations from inception up until December 11th, 2016 (Table S2). Two additional sources (Google Scholar and ISRCTN registry) were manually searched for additional trials or protocols by the same author. Authors of included trials with large sample size were also contacted for additional data (Table S3). No limitations concerning language, publication year or status were applied. The reference lists of the included trials and relevant reviews were manually searched as well.

Study selection, data collection, and risk of bias in individual studies

Titles, abstracts, and full texts of studies identified from the literature search were screened by one author (DV) with a subsequent duplicate independent checking against the eligibility criteria by two other authors (DK, SNP), while conflicts were resolved by the last author (TE). The same protocol was applied for the extraction of study characteristics (study design, setting, country, and language; patient number, sex, age, and malocclusion; extraction protocol; orthodontic appliance, anchorage, and duration; outcome assessed; conflict of interest) and numerical data using pre-determined and piloted extraction forms. Piloting of the forms was performed during the protocol stage until over 90% agreement was reached.

The risk of bias in the included randomized and non-randomized studies was assessed using Cochrane's risk of bias tool (25) and the Downs and Black (27) tool (Table S4), respectively, based on guidance from the Cochrane Handbook (25).

Data synthesis

The primary outcome for the meta-analysis was the sagittal position of the lower lip, measured cephalometrically with its distance from the E plane (LL-EL). Secondary outcomes included the distance of the upper lip from the E plane (UL-LL), the nasolagiabial angle (NLA), and the soft tissue profile convexity angle excluding the nose (SPC; measured as soft nasion – subnasale – soft pogonion). Additionally, the patient-relevant outcome of esthetic profile assessment by a panel was included.

As the effects of orthodontic fixed appliance treatment is bound to be affected by many factors, including type of orthodontic appliances, treatment duration, and biological patient profile (28–30), a random-effects model was deemed appropriate to encompass this variability and calculate the average distribution of true effects among studies. The novel Paule-Mandel random-effects estimator was used instead of the DerSimonian and Laird one, based on recent guidance (31).

Mean Differences (MD) of treatment-induced changes (post- minus pre-treatment) with their corresponding 95% Confidence Intervals (CI) were chosen as effect measures from continuous outcomes. Standardized Mean Differences (SMD) were used to pool together different panel-reported scales used to assess profile esthetics. SMDs were also calculated to assess how different Ex and Non-Ex groups were at baseline for each of the four outcomes, for baseline sagittal upper incisor position, and for the amount of treatment-induced upper incisor retraction (Supplement 1).

Absolute and relative between-trial heterogeneity was quantified with the tau^2 metric and the I^2 statistic, respectively. The latter is defined as the proportion of total variability in the results explained by heterogeneity, and not chance (22). 95% CIs around all heterogeneity measures were calculated to quantify existing uncertainty. 95% predictive intervals (PrIs) were calculated for meta-analyses of three trials or more, to incorporate existing heterogeneity and provide a clinically-relevant range of possible effects for a future clinical setting (32). All analyses were run in Stata SE 14.0 (StataCorp, College Station, TX) by one author (SNP). A two-tailed P-value of 0.05 was considered significant for hypothesis-testing, except for a 0.10 used for the test of heterogeneity and reporting biases, due to low power (33).

Additional analyses and risk of bias across studies

Possible sources of heterogeneity were a priori planned to be sought through mixed-effects subgroup analyses and random-effects meta-regression for meta-analyses of ≥ fives studies, including: mean patient age, % male proportion of the patient sample, and amount of incisor retraction during treatment (Supplement 1). Indications of reporting biases (including small-study effects and publication bias) were performed for meta-analyses of ≥ 10 studies (34) using contour-enhanced funnel plots and Egger's test (35). The overall quality of evidence (confidence in effect estimates) for each outcome was rated using the GRADE approach (23). The minimal clinical important, large, and very large effects were defined a priori (Supplement 1) and used to augment the produced forest plots with contours of effect magnitude (36). Robustness of the results was checked through a sensitivity analysis controlling indirectly for systematic baseline differences between the compared Ex and Non-Ex groups (confounding), by including only studies with only small or moderate differences (SMD≤0.5; Supplement 1).

Results

Study selection

The literature search yielded a total of 1,006 hits (Fig. 1), 104 of which proceeded to full text assessment after eliminating duplicates and ineligible studies by title or abstract (Table S5). Finally, a total of 65 papers were identified as eligible for inclusion in the present systematic review. After pooling multiple journal papers / dissertations relating to the same study a total of 52 unique clinical studies published in English, Chinese, German, Indonesian, Korean, or Portuguese between 1987 and 2016 were included. Apart from data from published reports, a total of 11 authors of identified studies with large sample size (≥80 patients) were contacted for raw data to reanalyze, however only two answered, from which one provided raw data (37).

Study characteristics

The descriptive characteristics of the 52 included studies can be seen in Table S6. From these, only 1 (2%) was a randomized trial, 2 (4%%) were prospective non-randomized cohort studies, and the remaining 49 (94%) were non-randomized studies of unclear or retrospective design. Most studies were conducted in university clinics or private practices in at least 13 different countries. Overall, 1,876 patients were included with a mean age of 14.0 years (from the 28 studies reporting age) and with 31.2% of the patients being male (from the 22 studies reporting sex). The majority of included studies assessed angular and/or linear variables from analysis of lateral cephalograms, while four studies assessed profile esthetics of Ex and Non-Ex patients.

Risk of bias within studies

The risk of bias assessment is separately reported in Table S7 for the identified randomized trial and in Table S8 & Fig. 2 for the identified non-randomized trials. The randomized trial was judged as being in high risk of bias, due to issues in the random allocation of patients in groups, the lack of outcome assessor blinding, and the lack of generalizability to the average patient. Likewise, all non-randomized studies presented a high risk of bias for at least one domain, with the most problematic ones being lack of blinding, data dredging or multiple testing, baseline confounding, and incomplete reporting. Incomplete reporting was of particular interest, as it precluded in many instances the use of patient- or treatment-related characteristics as covariates in the planned subgroup analyses.

Data synthesis

Most of the analyses were based on the data included in the published report. The only exception was the study of Bowman and Johnson (37), where the authors provided raw data for re-analysis (Table S9-S11). The results indicated that extraction treatment was associated with an additional retraction of the lower lip from the E plane by 1.9 mm (95% CI=1.2 to 2.6 mm) and at the same time with a more esthetically favorable profile by 4.4 Visual Analogue Scale (VAS) points (95% CI=0.5 to 8.4) than non-extraction treatment (Table S10). However, discernable differences in facial esthetics were higher among dentists' panels than among laypersons' (differences of 8.3 and 3.0 VAS points, respectively). Also extraction of two premolars was associated with less retraction of the lower lip and more favorable facial esthetics than the extraction of four premolars (Table S11).

Meta-analyses were performed initially by pooling together separate experimental arms provided by each study to compare any Ex protocol to Non-Ex treatment. As however, the results were highly heterogeneous (Table S12), a separate analysis distinguishing between the Ex subgroups of 2 premolars (2PM) and 4 premolars (4PM) was ultimately included (Table 1).

As far as the primary outcome is concerned, Ex treatment was associated with an additional retraction of the lower lip compared to Non-Ex treatment (Fig. 3a), which was significant only for the Ex of 4PMs (MD=-2.0 mm; 95% CI=-2.4 to -1.3).

The position of the upper lip was likewise not significantly affected by Ex of 2PMs, but only by Ex protocols of 4PMs, where an additional upper lip retraction was found (MD=-1.4 mm; -2.0 to -0.7 mm) compared to Non-Ex treatment (Fig. 3b). The NLA was significantly increased compared to Non-Ex protocols by the Ex of either 2PMs (MD=2.4º; 95% CI=0.9 to 3.9º) or 4PMs (MD=4.4º; .0 to 5.9º; Fig. 3c). On the otherhand, Ex treatment of 4PMs – but not 2PMs – was associated with an increase of the SPC compared to Non-Ex treatment (MD=1.8º; 95% CI=0.8 to 2.9º; Fig. 3d). Finally, Ex profiles were judged as more esthetically pleasing than Non-Ex profiles by mixed panels (SMD=0.4; 95% CI=0.2 to 0.6), although this was mainly discerned by dentists and not laypersons (SMDs of 0.7 and 0.3, respectively; Table 2).

Significant differences were observed between the 2PM and the 4PM subgroup for the outcomes of LL-EL and SPC, where the latter had a significantly greater impact on the facial profile (Table 1). However, both absolute and relative heterogeneity remained high for four of the meta-analyses, even after breaking the analysis into subgroups of 2PMs and 4PMs ($tau^2 > 1.0$ and $I^2>75\%$). Therefore, further sources of heterogeneity were attempted to be explained through meta-regressions and subgroup analyses (Table 3; Table S13-S14; Fig.S1). No effect was found for patient age or sex on the response to Ex treatment, apart from NLA, where a significantly greater increase of the NLA was seen for older Ex patients (by 0.6º per patient year) compared to Non-Ex patients. Additionally, among studies with 4PM Ex, significant differences were seen between Ex of four first and Ex of four second PMs, where the latter were associated with greater increase of the SPC angle (Table S13). Finally, the amount of incisor retraction during treatment was significantly associated with extraction effects with an additional 0.7 mm of lower or upper lip retraction and an additional 1.6º of NLA increase for each additional mm of upper incisor retraction (Table 3; Fig. S1). This is important since orthodontic extractions can be performed for a wide variety of indications and the effect of post-extraction insicor retraction during treatment explains part of this heterogeneous soft tissue response.

A number of sensitivity analyses were conducted to assess the robustness of the analyses to methodological characteristics, with most finding no significant thread to the results' validity and no signs of reporting bias (Egger's test non-significant in all cases). However, baseline differences between the compared Ex and Non-Ex groups had a significant influence on the reported changes of the upper and the lower lip (Fig. S1), which indicated baseline confounding. Therefore, all meta-analyses were performed by including only a subset of identified studies that had relatively comparable groups at baseline for each outcome (SMD≤0.5; Table 4; Fig. S2-S6). Extraction effects on the profile were slightly less pronounced in the sensitivity analysis than the original analysis, although the differences were small.

The GRADE assessment using the more consistent meta-analyses from the sensitivity analysis were judged to be of very low quality according to GRADE (Table 5; Table S15), due to the inclusion of non-randomized studies with methodological limitations, inconsistency and imprecision. A dose-response relationship was observed between lip retraction and incisor retraction, but GRADE was not upgraded, due to the abovementioned issues.

Discussion

The present systematic review summarizes evidence from clinical studies comparing the effects of extraction and non-extraction fixed appliance treatment on the soft tissue profile. Overall a total of 52 clinical cohort studies published in the last 30 years and comparing 1876 patients treated with systematic extraction protocol or non-extraction protocol were identified, though subsequently, only studies with premolar extractions were analyzed quantitatively.

The results of the meta-analyses indicated that extraction treatment potentially impacted the soft tissue profile of patients, with changes being more pronounced in the four-premolar extraction protocol compared to the two-premolar extraction protocol (Table 1). Extraction of four premolars lead to significantly greater retraction of the upper/lower lip from Rickett's E plane, as well as increased nasolabial angle and the soft tissue profile convexity excluding the nose compared to non-extraction treatment. On the other hand, extraction of four premolars led only to a statistically significant increase of the nasolabial angle. However, it must be noted that a considerably heterogeneous soft tissue response was observed, which means that tooth extractions could not consistently predict a retraction of the upper/lower lip or an increase of the nasolabial angle and the profile convexity (as the 95% PrI included both negative and positive values). This agrees with historical articles in orthodontics on the pattern and unpredictability of soft tissue response after tooth extractions and incisor retraction (38).

As far as subjective outcomes are concerned, orthodontic extraction treatment was associated that with statistically significantly more pleasing face esthetics compared to non-extraction treatment (Table 2). The clinical relevance however of this questionable, since the magnitude of this esthetic advantage was weighted unequally as moderate and small by dentists and laypersons, respectively. This can be most safely attributed to either a baseline skeletal/dental protrusion that is accommodated to a more pleasant profile through extraction treatment (37) or as an induced protrusion resulting from non-extraction treatment, but the quality of evidence is very low due to bias and caution is warranted.

Considerable heterogeneity was seen in the effects of extraction treatment on the facial profile, with a wide variety of patient-, treatment-, or study-related factors explaining part of it. First of all, a significant association was seen between patient age and treatment-induced increase of the nasolabial angle through meta-regression (Table 3), with older patients showing a greater increase in the nasolabial angle than younger patients. This might be explained from either prolonged nasal growth up to adulthood or age-related changes of the lips (39).

Furthermore, both treatment-induced retraction of the lower / upper lip and treatment-induced increase of the nasolabial angle were found to be significantly associated with the retraction of the upper incisor during treatment (Table 3). This means that part of the greater soft tissue changes observed in extraction patients compared to non-extraction patients could be attributed to the upper incisor being more retracted among the former. This finding is of high clinical relevance for the orthodontist during the treatment planning stage, as it implies that extraction treatment might have a smaller impact to the facial profile if the incisors are retracted less during treatment (i.e. if extraction spaces are closed from posterior or if extractions are used to accommodate blocked out teeth). This finding agrees with previous studies of extraction patients that highlight the correlation between maxillary incisor retraction and soft tissue profile change (40–42), while at the same time commenting on the lack of predictability. The present study builds on the epidemiological robustness of these by integrating the response in the non-extraction groups, while also adding the effect of maxillary incisor retraction on the nasolabial angle.

Baseline lip thickness might be another important modifying factor for the soft tissue response to orthodontic extraction treatment. It has been reported that a correlation between treatment-induced incisor retraction and lip retraction exists mainly for patients with thin lips or high lip strain, but not for patients with thick lips or low lip strain (42–44). However, it must be also taken in consideration that lip thickness might also be influenced by incisor position (45). Unfortunately, only 7 studies identified in the present review reported on baseline lip thickness thickness and used three different cephalometric variables. As a result, no meta-regression could be performed to assess the influence of baseline lip thickness on treatment-induced lip retraction, as less than 5 studies used the same variable and the role of lip thickness or strain remains unclear.

Finally, the study design characteristics of the included studies were closely related to the studies' results, and specifically to baseline imbalances between extraction and non-extraction patients in the position of the upper or lower lip that were significantly associated with the amount of treatment-induced upper or lower lip retraction (Table S14). This could have direct bearing to the conclusions drawn from the present systematic review, as a large portion of the studies included in the meta-analyses compared patients that were at baseline vastly different (Fig. S2-S3). Therefore, sensitivity analyses were performed by including only relatively-matched studies with small to moderate baseline inbalances between extraction and non-extraction patients (Table 4), which indicated that extractions affected the facial profile less than in the original analyses. Therefore, clinical recommendations along the GRADE guidelines were based on the sensitivity analyses (Table 5), which were deemed less-biased. Empirical evidence of bias originating from lack of matching has been previously identified in orthodontic literature (46). Ideally, baseline homogenous groups can be attained in prospective studies by employing randomization (47). On the other hand, baseline similarity of samples in observational studies can also be ensured, using refined statistical methods like propensity scores / discrimant analyses (13, 15, 48, 49) to 'match' the compared samples and reduce bias (50). However, such methods are still not widely-employed in orthodontics (51) and should be considered in future studies.

The present systematic review has several advantages, since its protocol was registered a priori in PROSPERO, it employed wide unrestricted literature changes and robust methods, like the employment of iterative Paule-Mandel random-effects estimator that is less biased than the old DerSimonian-Laird one (52). Additionally, all post hoc deviations were listed in detail (Supplement 2) and the review's dataset was transparently provided (53). However, several limitations are also present. First and foremost, the present review is based on a sample of mostly non-randomized trials that are potentially biased (54), and especially retrospective ones, which are more biased than prospective ones (14). Additionally, the effects of extraction therapy on the facial profile were considerably heterogenous, and although parts of heterogeneity were explained by subgroup, meta-regression, and sensitivity analyses, heterogeneity should be taken into account during clinical decision-making.

The results of the present systematic review might be applicable to a wide patient clientele due to the number and diversity of included studies, which covered adult or adolescent patients treated in university clinics, private practices, and hospitals of thirteen countries in four different continents.

The present systematic review of controlled clinical evidence indicates that fixed appliance treatment with tooth extractions might be associated with soft tissue profile changes, the extent of which are dependent on patient age, extraction protocol, and treatment-associated retraction of the upper incisors. However, existing studies report heterogenous results and no consistent predictions of profile response can be made. The current evidence base is based on retrospective clinical studies of potentially compromised internal validity, due to their study design, methodological issues, incomplete reporting, and limited sample.

Future studies aiming to assess the effects of extractions on the facial profile should ideally adopt a prospective controlled design, calculate *a priori* the needed sample size for all outcomes, and report in full detail patient characteristics, used appliances/mechanics, dental effects, and quantitative results. Future studies should ideally ensure that compared groups are fully balanced for all known or unknown factors through randomization. In cases that randomization is not easily employed, future studies should at a minimum ensure that compared groups are a priori fully matched at baseline (for example through propensity scores or discriminant analysis) for all known important factors, including age, soft tissue profile, extraction protocol, treatment mechanics, and planned incisor retraction. A priori registration of the study protocol and subsequent making all measured data freely accessible can further enhance the transparency and reproducibility of research findings.

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Figure Legends

Fig. 1. Flowdiagram for the identification and selection of studies in this systematic review.

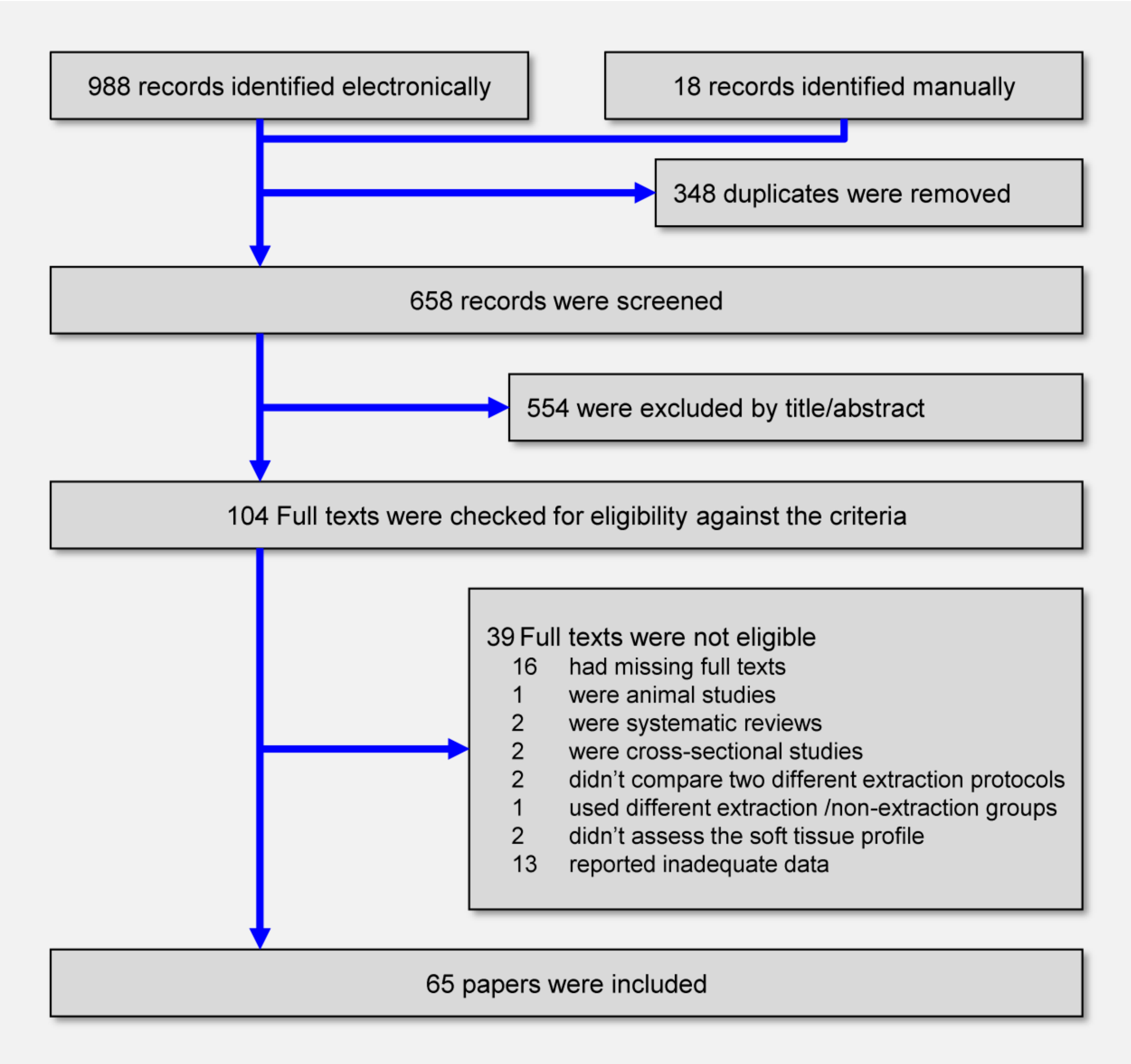


Fig. 2. Summary of the risk of bias of included non-randomized studies.

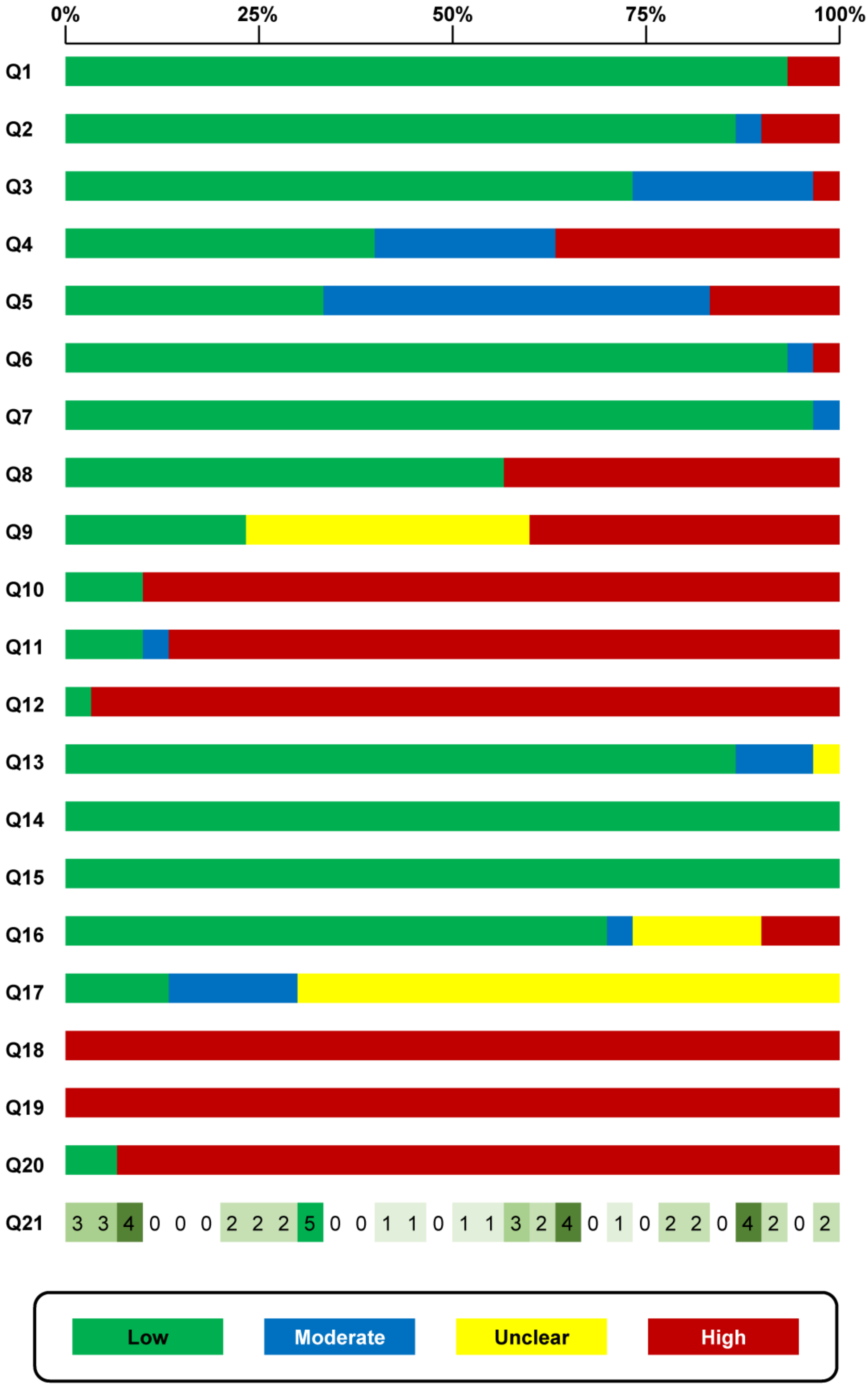


Fig. 3a. Forest plot on change of lower lip - E plane distance in extraction and non-extraction treatment.

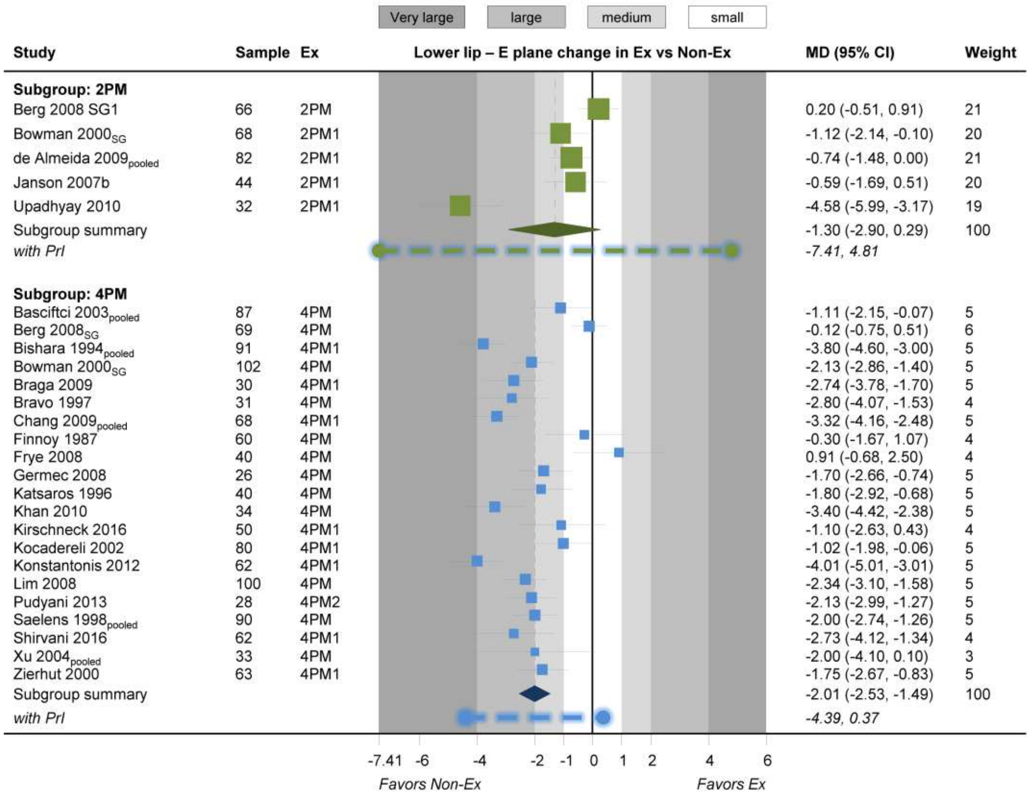


Fig. 3b. Forest plot on change of upper lip - E plane distance in extraction and non-extraction treatment.

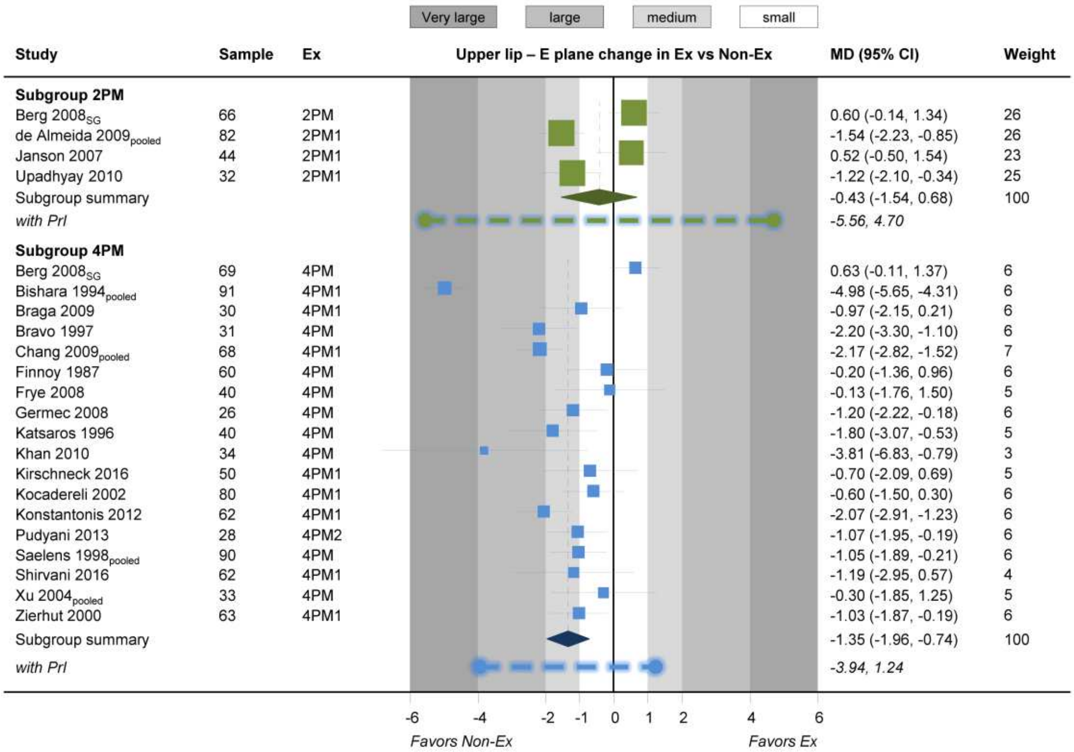


Fig. 3c. Forest plot on change of nasolabial angle in extraction and non-extraction treatment.

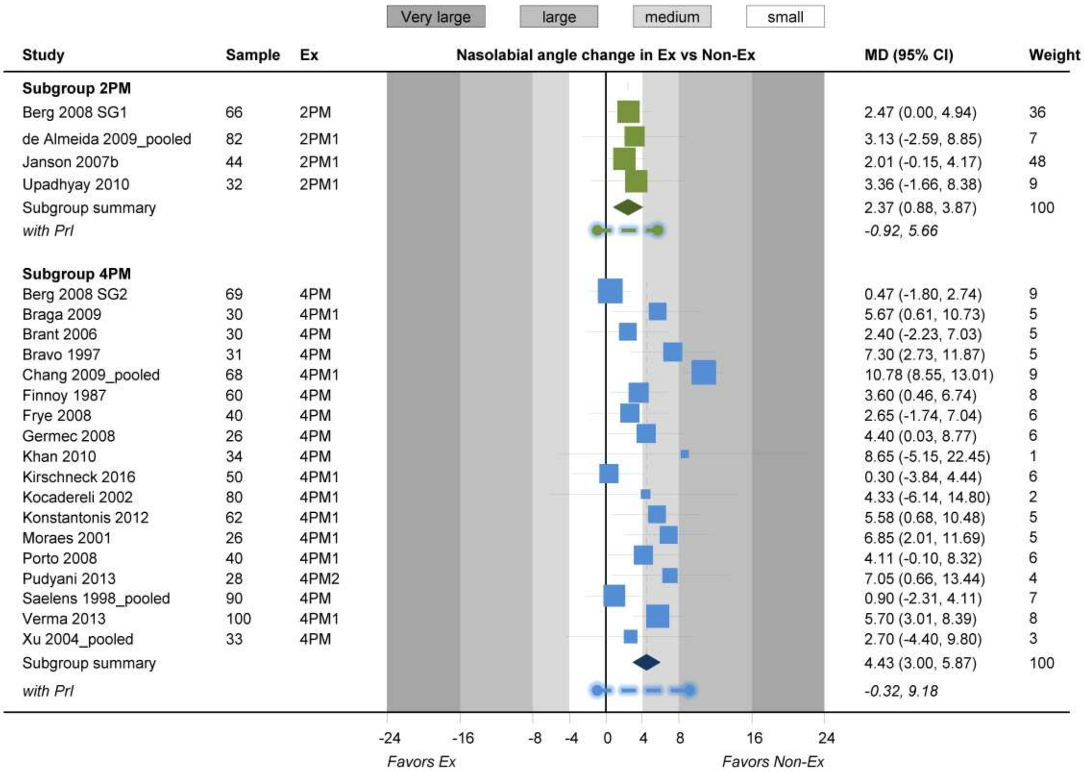
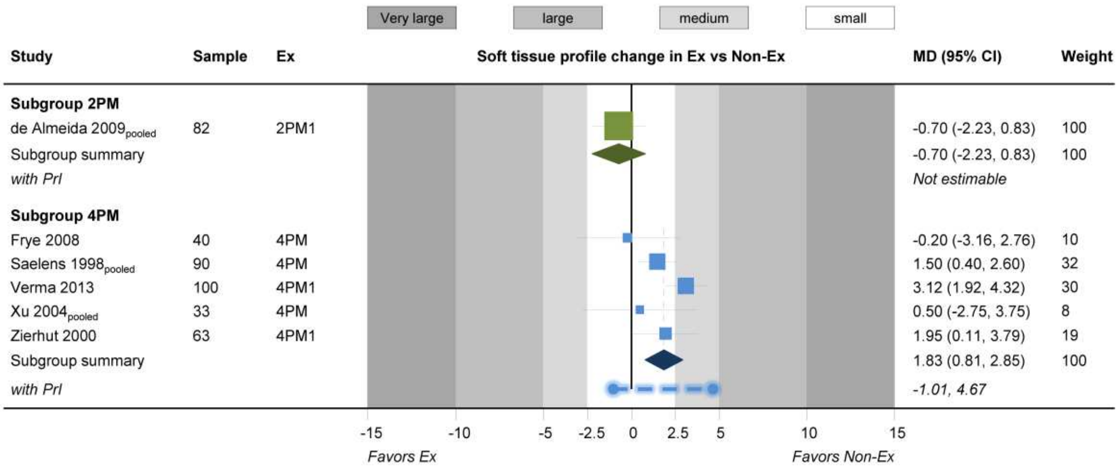


Fig. 3d. Forest plot on change of soft tissue profile convexity angle in extraction and non-extraction treatment.



Soft tissue changes in extraction versus non-extraction treatment with fixed orthodontic appliances: a systematic review and meta-analysis

Supplement

Table S1. List of inclusion and exclusion criteria.

Field	Inclusion	Exclusion
Patients	Patients of any age, sex, ethnicity, and malocclusion.	▪ Animal studies ▪ In vitro studies
Intervention	Orthodontic treatment with fixed appliances and any systematic extraction protocol (excluding the extraction of third molars).	▪ Patient not receiving orthodontic treatment. ▪ Patients receiving partial appliances.
Comparison	Patients similar to the intervention group treated with: ▪ a different systematic extraction protocol other than the Invervention group or ▪ a non-extraction protocols	
Outcome	Quantitative soft-tissue parameters including cephalometric parameters or panel assessments shortly after treatment.	▪ No soft tissue profile-related outcomes. ▪ Inadequate reporting making data synthetis impossible.
Study design	Randomized controlled trials or non-randomized prospective / retrospective studies.	

Table S2. The electronic databases searched, the search strategy used, and the corresponding results (as of December 11th, 2016).

Database	Site	Search strategy	Limit	Hits
PubMed	http://www.ncbi.nlm.nih.gov/pubmed/	orthodon* AND extract*[Title] AND ("soft tissue" OR profile OR lip OR nasolabial OR mentolabial)	Humans	152
Cochrane Library (CDSR/DARE)	http://onlinelibrary.wiley.com/cochranelibrary/search/	orthodon* AND extract* AND ("soft tissue" OR profile OR lip OR nasolabial OR mentolabial)	-	1
Cochrane Library (CENTRAL)	http://onlinelibrary.wiley.com/cochranelibrary/search/	orthodon* AND extract* AND ("soft tissue" OR profile OR lip OR nasolabial OR mentolabial)	-	21
Embase		orthodon* AND extract* AND ("soft tissue" OR profile OR lip OR nasolabial OR mentolabial)	Humans	131
Virtual Health Library	http://pesquisa.bvsalud.org/portal/advanced/?lang=en	orthodon* AND extract* AND ("soft tissue" OR profile OR lip OR nasolabial OR mentolabial)	-	92
Scopus	http://www.scopus.com/	orthodon* AND extract* AND ("soft tissue" OR profile OR lip OR nasolabial OR mentolabial)	Limit: Dentistry Human Exclude: Review Case report Histology	166
ISI Web of Knowledge	http://apps.webofknowledge.com	orthodon* AND extract* AND ("soft tissue" OR profile OR lip OR nasolabial OR mentolabial)	Research area: dentistry oral surgery medicine Exclude: Case report Review	425
ClinicalTrials.gov	https://clinicaltrials.gov/	orthodon* AND extract* AND ("soft tissue" OR profile OR lip OR nasolabial OR mentolabial)	-	0
SUM				988

Table S3. Email communication attempts with authors of included studies with ≥80 patients.

Nr	Paper	Contact Author	Status
1	Bowman SJ, Johnston LE, Jr. The esthetic impact of extraction and nonextraction treatments on Caucasian patients. Angle Orthod 2000;70(1):3-10.	S. Jay Bowman Kalamazoo Orthodontics, Portage, MI	Sent Oct 2; Replied Oct 3; Sent raw data.
2	Chung DH, Suk CK, Woo LJ, 이세형, 이상민. The Esthetic Impact of Extraction and Nonextraction Treatments on Korean People. Journal of Dental Rehabilitation and Applied Science. 2013;29(2):119-26.	Dong-Hwa Chung Department of Orthodontics and the Graduate School of Dentistry, Dankook University, Cheonan, Korea	Sent Oct 2; response pending.
3	Erdinc AE, Nanda RS, Dandajena TC. Profile changes of patients treated with and without premolar extractions. Am J Orthod Dentofacial Orthop 2007;132(3):324-31.	T.C. Dandajena Department of Orthodontics, University of the Witwatersrand, Johannesburg	Sent Oct 2; response pending.
4	Lim HJ, Ko KT, Hwang HS. Esthetic impact of premolar extraction and nonextraction treatments on Korean borderline patients. Am J Orthod Dentofacial Orthop 2008;133(4):524-31.	Hyeon-Shik Hwang Chonnam National University, Gwangju, Korea	Sent Oct 2; response pending.
5	Lin PT, Woods MG. Lip curve changes in males with premolar extraction or nonextraction treatment. Australian orthodontic journal. 2004;20(2):71-86. Moseling KP, Woods MG. Lip curve changes in females with premolar extraction or nonextraction treatment. Angle Orthod 2004;74(1):51-62.	Michael Woods Orthodontic Unit, School of Dental Science, The University of Melbourne, Melbourne, Australia	Sent Oct 2; response pending.
6	Saelens NA, De Smit AA. Therapeutic changes in extraction versus non-extraction orthodontic treatment. Eur J Orthod. 1998;20(3):225-36.	Nathalie A. Saelens Private Practice, Bloemenstraat 20, Yper, Belgium	Sent Oct 2; response pending.
7	Verma SL, Sharma VP, Tandon P, Singh GP, Sachan K. Comparison of esthetic outcome after extraction or nonextraction orthodontic treatment in class II division 1 malocclusion patients. Contemp Clin Dent 2013;4:206-12.	Sneh Lata Verma Chandra Dental College and Hospital, Barabanki, Uttar Pradesh, India	Sent Oct 2; response pending.
8	Weyrich C, Lisson JA. The effect of premolar extractions on incisor position and soft tissue profile in patients with class II, Division 1 Malocclusion. J Orofac Orthop 2009;70(2):128-38.	J.A. Lisson Department of Orthodontics, University Hospital and Dental Medical School Saarland, Homburg/Saar, Germany	Sent Oct 2. Responded Oct 3; said he won't provide data.
9	Basciftci FA, Usumez S. Effects of extraction and nonextraction treatment on class I and class II subjects. Angle Orthod 2003;73(1):36-42.	Faruk Ayhan Basciftci Department of Orthodontics, Selcuk University, Konya, Turkey	Sent Oct 3; response pending.
10	Kocadereli I. Changes in soft tissue profile after orthodontic treatment with and without extractions. Am J Orthod Dentofacial Orthop 2002;122(1):67-72.	Iken Kocadereli Orthodontic Department, Hacettepe Unversity, Ankara, Turkey	Sent Oct 3; response pending.
11	Kumari M, Fida M. Vertical facial and dental arch dimensional changes in extraction vs. non-extraction orthodontic treatment. J College of Physicians and Surgeons--Pakistan : JCPSP. 2010;20(1):17-21.	Mubassar Fida Orthodontics, Section of Dentistry, Dept. of Surgery, The Aga Khan University Hospital, Stadium Road, Karachi	Sent Oct 3; response pending.

Table S4. Guidance followed on using the risk of bias tool for non-randomized studies.

Q	Question	Description
Q1	Clear hypothesis/aim/objective clearly described	
Q2	Main outcomes to be measured clearly described	
Q3	Characteristics of the patients clearly described	Including patient age, sex, and malocclusion.
Q4	Treatment clearly described	Including extraction protocol, used appliance, anchorage management, and treatment duration.
Q5	Distributions of confounders/group described	Including malocclusion severity, treatment duration, and baseline pre-treatment outcome data.
Q6	Main findings of the study clearly described	
Q7	Estimates of the random variability in outcome data	Either standard deviations or standard errors.
Q8	Actual P values reported	Except for P< .001
Q9	Representative sample of the population included?	
Q10	Made an attempt to blind outcome measurement	
Q11	Made clear any results that were based on "data dredging" or multiple testing	
Q12	Adjusted for different lengths of follow-up of patients	
Q13	Appropriate statistical tests	
Q14	Reliable compliance with the intervention/s	
Q15	Accurate main outcome measures	
Q16	Patients in Ex/ NonEx recruited from the same population	
Q17	Patients in Ex/ NonEx recruited over the same time-period	
Q18	Patients randomised to Ex/ NonEx groups	
Q19	Randomization concealed from patients/ staff	
Q20	Adjustment for confounding	Including patient age, sex, and baseline outcome data.
Q21	Sufficient power to detect a clinically important effect	Based on most cephalometric profile variables. Sample size/study group: ▪ <20 patients: 0 point ▪ 20-29 patients: 1 point ▪ 30-39 patients: 2 points ▪ 40-49 patients: 3 points ▪ 50-59 patients: 4 points ▪ ≥ 60 patients: 5 points

Ex, extraction group; NonEx, non-extraction group.

Supplement 1. Additional details on the review methodology.

Data synthesis

Standardized Mean Differences (SMD) were used to assess how comparable (or not) were the Ex and Non-Ex group in each of the included studies for the four outcomes: LL-EL, UL-EL, NLA, SPC. For this, the baseline means and Standard Deviations (SD) of Ex and Non-Ex groups were used. Small, moderate, large, and very large effects for Standardized Mean Differences (SMD) were conventionally defined in the review protocol using the cut-offs of 0.2, 0.5, and 0.8 [Schünemann et al., 2008]. We arbitrarily defined studies as having baseline discrepancies, when the Ex / Non-Ex groups had small or moderate differences at baseline for an outcome (SMD ≤ 0.5). This was used to perform sensitivity analyses according to baseline confounding in the identified studies.

The same protocol was used to assess baseline discrepancies between Ex & Non-Ex groups for the sagittal position of the upper incisors. For this, the baseline means and SDs for identified cephalometric measurements of upper incisor position with reference to several planes (Nasion-A point, A point-Pogonion, pterygoid vertical, or sella perpendicular) were pooled in a homogenous scale using the SMD. This was used to perform sensitivity analyses according to baseline confounding in the identified studies.

Additionally, the SMD was used to assess differences between Ex & Non-Ex groups in the standardized amount of upper incisor retraction by taking the post-treatment minus pre-treatment difference. This was used to perform subgroup analyses of soft tissue extraction effects according to the amount of upper incisor retraction (as a proxy to space closure from anterior) being made.

GRADE approach

The minimal clinical important, large, and very large effects for Mean Differences (MD) were conventionally defined in the review protocol as half [Norman et al., 2004], one, and two standard deviations, respectively (using the standard deviation of the cephalometric norm). Small, moderate, large, and very large effects for Standardized Mean Differences (SMD) were conventionally defined in the review protocol using the cut-offs of 0.2, 0.5, and 0.8 [Schünemann et al., 2008]. Finally, the optimal information size (i.e. required meta-analysis sample size) was calculated for each outcome independently for $\alpha = 5\%$ and $\beta = 20\%$.

References to Supplement 1

Norman GR, Sloan JA, Wyrwich KW. The truly remarkable universality of half a standard deviation: confirmation through another look. *Expert Rev Pharmacoecon Outcomes Res* 2004; **4**: 581–585.

Schünemann H, Brozek J, Oxman A, eds. GRADE handbook for grading quality of evidence and strength of recommendation. Version 3.2. The GRADE Working Group; 2009. [updated March 2009] http://www.who.int/hiv/topics/mtct/grade_handbook.pdf.

Table S5. List of included and excluded studies, with the corresponding reasons.

Nr	Paper	Status
1	Almasri M. Reconstruction of the alveolar cleft: effect of preoperative extraction of deciduous teeth at the sites of clefts on the incidence of postoperative complications. The British journal of oral & maxillofacial surgery. 2012;50(2):154-6. Epub 2011/02/01.	Excluded by title
2	Almeida NV, Silveira GS, Pereira DM, Mattos CT, Mucha JN. Interproximal wear versus incisors extraction to solve anterior lower crowding: a systematic review. Dental press journal of orthodontics. 2015;20(1):66-73. Epub 2015/03/06.	Excluded by title
3	Amato F, Mirabella AD, Macca U, Tarnow DP. Implant site development by orthodontic forced extraction: a preliminary study. The International journal of oral & maxillofacial implants. 2012;27(2):411-20. Epub 2012/03/24.	Excluded by title
4	Barbosa VL. Angle Class I malocclusion treated with lower incisor extraction. Dental press journal of orthodontics. 2013;18(3):150-8. Epub 2013/10/08.	Excluded by title
5	Battagel JM. Discriminant analysis: a model for the prediction of relapse in Class III children treated orthodontically by a non-extraction technique. Eur J Orthod. 1993;15(3):199-209. Epub 1993/06/01.	Excluded by title
6	Baumrind S, Korn EL, Boyd RL, Maxwell R. The decision to extract: part II. Analysis of clinicians' stated reasons for extraction. Am J Orthod Dentofacial Orthop 1996;109(4):393-402. Epub 1996/04/01.	Excluded by title
7	Bishara SE, Cummins DM, Jakobsen JR. The morphologic basis for the extraction decision in Class II, division 1 malocclusions: a comparative study. Am J Orthod Dentofacial Orthop 1995;107(2):129-35. Epub 1995/02/01.	Excluded by title
8	Cardaropoli D, Debernardi C, Cardaropoli G. Immediate placement of implant into impacted maxillary canine extraction socket. The International journal of periodontics & restorative dentistry. 2007;27(1):71-7. Epub 2007/03/21.	Excluded by title
9	Chae JM. Unusual extraction treatment of Class I bialveolar protrusion using microimplant anchorage. Angle Orthod 2007;77(2):367-76. Epub 2007/02/27.	Excluded by title
10	Checchi V, Savarino L, Montevecchi M, Felice P, Checchi L. Clinical-radiographic and histological evaluation of two hydroxyapatites in human extraction sockets: a pilot study. International journal of oral and maxillofacial surgery. 2011;40(5):526-32. Epub 2011/02/02.	Excluded by title
11	Chen LL, Duan YZ, Li RX, Wang HX, Xu LL, Bi HX. [Clinical research on unilateral extraction for moderate crowding]. Zhonghua kou qiang yi xue za zhi = Zhonghua kouqiang yixue zazhi = Chinese journal of stomatology. 2004;39(2):100-3. Epub 2004/04/06.	Excluded by title
12	Chen LL, You QL, Yang YM. [Non-extraction treatment in borderline class III malocclusion]. Shanghai kou qiang yi xue = Shanghai journal of stomatology. 2011;20(1):82-7. Epub 2011/04/01.	Excluded by title
13	Chen SX, Tang GH, Jiang YN, Gu YJ, Zhang T, Gao MQ. [Clinical effect of premolar extraction with high torque self-locking appliances]. Shanghai kou qiang yi xue = Shanghai journal of stomatology. 2015;24(6):739-42. Epub 2016/04/12.	Excluded by title
14	de Souza DR, Semeghini TA, Kroll LB, Berzin F. Oral myofunctional and electromyographic evaluation of the orbicularis oris and mentalis muscles in patients with class II/1 malocclusion submitted to first premolar extraction. Journal of applied oral science : revista FOB. 2008;16(3):226-31. Epub 2008/12/18.	Excluded by title
15	Deli R, Di Gioia E, Galantucci LM, Percoco G. Automated landmark extraction for orthodontic measurement of faces using the 3-camera photogrammetry methodology. The Journal of craniofacial surgery. 2010;21(1):87-93. Epub 2010/01/15.	Excluded by title
16	Duan Y, Zhang Y, Sun Y. [Treatment of Class II division 1 extraction cases by use of edgewise technique]. Zhonghua kou qiang yi xue za zhi = Zhonghua kouqiang yixue zazhi = Chinese journal of stomatology. 2000;35(6):417-9. Epub 2002/01/10.	Excluded by title
17	Fan FY, Wang XX, Zhang J. [Study of chin morphology in Angle Class II division 2 malocclusion after non-extraction orthodontic treatment]. Shanghai kou qiang yi xue = Shanghai journal of stomatology. 2011;20(6):653-7. Epub 2012/01/14.	Excluded by title
18	Ferro F, Perillo L, Ferro A. Non extraction short-term arch changes. Progress in orthodontics. 2004;5:18-43. Epub 2004/08/27.	Excluded by title
19	Gerety RG. Non-extraction treatment: utilization of the lip bumper to establish the mandibular arch. Journal of general orthodontics. 1997;8(3):6-12. Epub 1998/03/24.	Excluded by title
20	Gomez CE. Non-extraction therapy in maxillary deficiency cases. The Functional orthodontist. 1997;14(1):15-8, 20-2. Epub 1997/01/01.	Excluded by title
21	Gong Y, Yu Q, Li PL, Wang HH, Wei B, Shen G. [Efficacy evaluation of fixed Twin-block appliance and tooth extraction in skeletal Class II malocclusion]. Shanghai kou qiang yi xue = Shanghai journal of stomatology. 2014;23(5):597-600. Epub 2014/12/30.	Excluded by title
22	Greatrex PA, Sampson WJ, Richards LC, Twelftree CC. The extraction of permanent second molars and its effect on the dentofacial complex of patients treated with the Tip-Edge appliance. Eur J Orthod. 2002;24(5):501-18. Epub 2002/11/01.	Excluded by title
23	Grob DJ. Extraction of a mandibular incisor in a Class I malocclusion. Am J Orthod Dentofacial Orthop 1995;108(5):533-41. Epub 1995/11/01.	Excluded by title
24	Harzer W, Seifert D, Eckardt L. Indications for compensatory extractions in orthodontic space closure in the frontal segments. J Orofac Orthop 1996;57(6):324-33. Epub 1996/12/01.	Excluded by title
25	Hegde C, Hegde M. Mandibular incisor extractions in orthodontics: pitfalls and triumphs: a report of three cases. International journal of orthodontics (Milwaukee, Wis). 2014;25(2):17-20. Epub 2014/08/12.	Excluded by title
26	Hodges A, Rossouw PE, Campbell PM, Boley JC, Alexander RA, Buschang PH. Prediction of lip response to four first premolar extractions in white female adolescents and adults. Angle Orthod 2009;79(3):413-21. Epub 2009/05/06.	Excluded by title
27	Isik F, Sayinsu K, Nalbantgil D, Arun T. A comparative study of dental arch widths: extraction and non-extraction treatment. Eur J Orthod. 2005;27(6):585-9. Epub 2005/11/01.	Excluded by title
28	Jacobs C, Jacobs-Muller C, Hoffmann V, Meila D, Erbe C, Krieger E, et al. Dental compensation for moderate Class III with vertical growth pattern by extraction of the lower second molars. J Orofac Orthop 2012;73(1):41-8. Epub 2012/01/18.	Excluded by title
29	Jacobs C, Jacobs-Muller C, Luley C, Erbe C, Wehrbein H. Orthodontic space closure after first molar extraction without skeletal anchorage. J Orofac Orthop 2011;72(1):51-60. Epub 2011/04/13.	Excluded by title
30	Jager A, el-Kabarity A, Singelmann C. Evaluation of orthodontic treatment with early extraction of four second molars. J Orofac Orthop 1997;58(1):30-43. Epub 1997/02/01.	Excluded by title
31	Janson G, Janson M, Nakamura A, de Freitas MR, Henriques JF, Pinzan A. Influence of cephalometric characteristics on the occlusal success rate of Class II malocclusions treated with 2- and 4-premolar extraction protocols. Am J Orthod Dentofacial Orthop 2008;133(6):861-8. Epub 2008/06/10.	Excluded by title
32	Janson G, Simao TM, Barros SE, Janson M, de Freitas MR. Influence of the cephalometric characteristics on the occlusal success rate of Class II malocclusions treated with nonextraction or with two maxillary premolar extraction protocols. World journal of orthodontics. 2010;11(4):e63-71. Epub 2010/01/01.	Excluded by title
33	Jung SK, Kim TW. New approach for the diagnosis of extractions with neural network machine learning. Am J Orthod Dentofacial Orthop 2016;149(1):127-33. Epub 2016/01/01.	Excluded by title
34	Katsaros C. Profile changes following extraction vs. nonextraction orthodontic treatment in a pair of identical twins. J Orofac Orthop 1996;57(1):56-9. Epub 1996/02/01.	Excluded by title
35	Konstantonis D, Anthopoulou C, Makou M. Extraction decision and identification of treatment predictors in Class I malocclusions. Progress in orthodontics. 2013;14:47. Epub 2013/12/12.	Excluded by title
36	Kook YA, Park JH, Bayome M, Sa'aed NL. Correction of severe bimaxillary protrusion with first premolar extractions and total arch distalization with palatal anchorage plates. Am J Orthod Dentofacial Orthop 2015;148(2):310-20. Epub 2015/08/04.	Excluded by title

37	Kurz C. The use of lingual appliances for correction of bimaxillary protrusion (four premolars extraction). Am J Orthod Dentofacial Orthop 1997;112(4):357-63. Epub 1997/11/05.	Excluded by title
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631	Kim S-J, 김영석, 강승구, 이영준. A comparative study of pre- and post-treatment cephalometric measurements: Upper premolar extraction only vs. upper/lower premolar extraction groups. The Korean Journal of Orthodontics. 2007;37(6):421-31.	Included for outcome assessment
632	Kinzinger G, Frye L, Diedrich P. Class II treatment in adults: Comparing camouflage orthodontics, dentofacial orthopedics and orthognathic surgery - A cephalometric study to evaluate various therapeutic effects. Journal of Orofacial Orthopedics. 2009;70(1):63-91.	Included for outcome assessment
633	Kirschneck C, Proff P, Reicheneder C, Lippold C. Short-term effects of systematic premolar extraction on lip profile, vertical dimension and cephalometric parameters in borderline patients for extraction therapy-a retrospective cohort study. Clinical Oral Investigations. 2016;20(4):865-74.	Included for outcome assessment
634	Kocadereli I. Changes in soft tissue profile after orthodontic treatment with and without extractions. Am J Orthod Dentofacial Orthop 2002;122(1):67-72.	Included for outcome assessment
635	Konstantonis D. The impact of extraction vs nonextraction treatment on soft tissue changes in Class I borderline malocclusions. Angle Orthod 2012;82(2):209-17.	Included for outcome assessment
636	Kumari M, Fida M. Vertical facial and dental arch dimensional changes in extraction vs. non-extraction orthodontic treatment. J College of Physicians and Surgeons--Pakistan : JCPSP. 2010;20(1):17-21.	Included for outcome assessment
637	Lim HJ, Ko KT, Hwang HS. Esthetic impact of premolar extraction and nonextraction treatments on Korean borderline patients. Am J Orthod Dentofacial Orthop 2008;133(4):524-31.	Included for outcome assessment
638	Lin PT, Woods MG. Lip curve changes in males with premolar extraction or nonextraction treatment. Australian orthodontic journal. 2004;20(2):71-86.	Included for outcome assessment
639	Moraes LCd, Salgado JaP, Castilho JCdM, Moraes MELd. Análise do ângulo nasolabial, em pacientes tratados ortodonticamente, com ou sem extrações dos pré-molares. PGR: Pós-Grad Rev Fac Odontol São José dos Campos. 2001;4(3):21-8.	Included for outcome assessment
640	Moseling KP, Woods MG. Lip curve changes in females with premolar extraction or nonextraction treatment. Angle Orthod 2004;74(1):51-62.	Included for outcome assessment
641	Porto VS. Estudo cefalométrico dos efeitos do tratamento ortodôntico sem e com extrações nas estruturas dentoesqueléticas e tegumentares em dilicofaciais. 2008:187-.	Included for outcome assessment
642	Pudyani PS, Hanimastuti Y. Facial soft tissue profile on borderline class I malocclusion in orthodontic treatment with or without teeth extraction. Dent J (Maj Ked Gigi) 2013;46(4):179–184.	Included for outcome assessment
643	Saelens NA, De Smit AA. Therapeutic changes in extraction versus non-extraction orthodontic treatment. Eur J Orthod. 1998;20(3):225-36.	Included for outcome assessment
644	Sathekge RM. Long term soft tissue lip changes following orthodontic treatment. Master's Thesis, University of Witwatersrand, Johannesburg, 2005.	Included for outcome assessment
645	Shirvani A, Sadeghian S, Abbasi S. Prediction of lip response to orthodontic treatment using a multivariable regression model. Dental Research Journal. 2016;13(1):38-45.	Included for outcome assessment
646	Stephens CK, Boley JC, Behrents RG, Alexander RG, Buschang PH. Long-term profile changes in extraction and nonextraction patients. Am J Orthod Dentofacial Orthop 2005;128(4):450-7.	Included for outcome assessment
647	Upadhyay M, Yadav S, Nagaraj K, Uribe F, Nanda R. Mini-implants vs fixed functional appliances for treatment of young adult Class II female patients: A prospective clinical trial. Angle Orthodontist. 2012;82(2):294-303.	Included for outcome assessment
648	Upadhyay M. Dentoskeletal and soft tissue treatment effects of two different methods for treating Class II malocclusions. Master's Thesis, University of Connecticut, 2010.	Included for outcome assessment
649	Verma SL, Sharma VP, Tandon P, Singh GP, Sachan K. Comparison of esthetic outcome after extraction or nonextraction orthodontic treatment in class II division 1 malocclusion patients. Contemp Clin Dent 2013;4:206-12.	Included for outcome assessment
650	Verma SL, Sharma VP, Tandon P, Singh GP. The Impact of Extraction vs Nonextraction Treatment on Soft Tissue Profile in Borderline Class I Malocclusion: A Cephalometric Study. J Ind Orthod Soc 2014;48(1):47-53.	Included for outcome assessment
651	Weyrich C, Lisson JA. The effect of premolar extractions on incisor position and soft tissue profile in patients with class II, Division 1 Malocclusion. Journal of Orofacial Orthopedics. 2009;70(2):128-38.	Included for outcome assessment
652	Wholley CJ, Woods MG. The effects of commonly prescribed premolar extraction sequences on the curvature of the upper and lower lips. Angle Orthod 2003;73(4):386-95.	Included for outcome assessment

653	Xu TM, Liu Y, Huang W, Lin JX. [Cephalometric comparison of soft-tissue morphology between extraction and non-extraction orthodontic treatment in borderline cases]. Beijing da xue xue bao Yi xue ban = Journal of Peking University Health sciences. 2004;36(6):650-4.	Included for outcome assessment
654	Xu TM, Liu Y, Yang MZ, Huang W. Comparison of extraction versus nonextraction orthodontic treatment outcomes for borderline Chinese patients. Am J Orthod Dentofacial Orthop 2006;129(5):672-7.	Included for outcome assessment
655	Zafarmand AH, Zafarmand MM. Premolar extraction in orthodontics: Does it have any effect on patient's facial height?. J Int Soc Prevent Communit Dent 2015;5:64-8.	Included for outcome assessment
656	Zhang SF, Lin XP, Zheng ML. [Soft tissue changes of chin with different premolar extraction patterns]. Shanghai kou qiang yi xue = Shanghai journal of stomatology. 2009;18(5):475-9.	Included for outcome assessment
657	Zierhut EC, Joondeph DR, Artun J, Little RM. Long-term profile changes associated with successfully treated extraction and nonextraction Class II Division 1 malocclusions. Angle Orthod 2000;70(3):208-19.	Included for outcome assessment
658	Zimmer B, Gaida S, Dathe H. Compensation of skeletal Class III malocclusion by isolated extraction of mandibular teeth. Journal of Orofacial Orthopedics-Fortschritte Der Kieferorthopadie. 2016;77(2):119-28.	Included for outcome assessment
659	Berg C. Concerning the change in the incisor position and the facial profile in dependence to the therapeutic extraction of premolars in patients with Class II/1 malocclusion. Doctoral Dissertation, University of Saarland, Homburg/Saar, 2008.	Included for outcome assessment

Table S6. Characteristics of included studies.

Study	Design, setting, country, language	Patient no, (M/F), mean age	Ortho reason	Extraction category	Anchorage	Tx duration	Appliance; Ex closure	Outcome	Outcome timing	Conflict of interest
Akyalcin 2007	rNRS; Uni; TUR; EN	Ex: 25 (13/12); 12.6 yrs NEx: 24 (12/12); 12.5 yrs	$_s$Cl.I; ALD	(4) 2xU4/2xL4	NR	Ex: 27.0 mos NEx: 24.2 mos	0.018"; NR	LCp; ceph (DSR)	Pre/Post Tx	Funding; non-profit
Allgayer 2010; 2011a,b	rNRS; pract; BRA; EN	Ex1: 22 (NR); NR Ex2: 43 (NR); NR Ex3: 22 (NR); NR	Various	Ex1: (2) 2xU4 Ex2: (4) 2xU4/2xL4 Ex3: (4) 2xU4/2xL5	NR	0.022" system	0.022"; sliding mechs$_{19x25SS}$	AV/LV; ceph	Pre/Post Tx	None existing
Aydemir 2014	rNRS; Uni; TUR; EN	Ex: 20 (0/20); 15.7 yrs NEx: 20 (0/20); 15.4 yrs	Cl.II/2; ALD	(4) 2xU4/2xL4	Ex: elastics NEx: elastics/ RT	Ex: 31.2 mos NEx: 20.4 mos	Roth; sliding mechs	AV/LV; ceph	Pre/Post Tx	NR
Basciftci 2003	rNRS; Uni; TUR; EN	Cl.I Ex: 22 (9/13); 14.5 yrs Cl.II Ex: 20 (7/13); 17.4 yrs Cl.I NEx: 25 (10/15); 13.6 yrs Cl.II NEx: 20 (8/12); 12.7 yrs	Cl.I & II	(4) 4xPM	NR	Cl I Ex: 22.3 mos Cl II Ex: 24.5 mos Cl I NEx: 19.1 mos Cl II NEx: 23.3 mos	NR; NR	AV/LV; ceph	Pre/Post Tx	NR
Berg 2008; Weyrich 2009[$]	uNRS; Uni; DEU; EN	Ex1: 34 (NR); 13.1 yrs Ex2: 37 (NR); 11.3 yrs NEx: 32 (NR); 9.6 yrs	Cl.II/1	Ex1: (2) 2xUPM Ex2: (4) 4xPM	Ex4/NEx: RFA; elastics	Ex1: 38.6 mos Ex2: 41.9 mos NEx: 46.6 mos	NR; NR	LV; ceph	Pre-Post Tx	NR
Bishara 1994; 1995a,b; 1997a,b; Cummins 1995[†]	uNRS; Uni; USA; EN	Ex: 44 (21/23); 11.6 yrs NEx: 47 (20/27); 11.4 yrs	Cl.II/1	(4) 2xU4/2xL4	HG	Ex: 35.9 mos NEx: 27.6 mos	EA; NR	AV/LV; ceph Front/lat. Phot.	Pre/Post/+2yr s	NR
Boley 1998	uNRS; pract; USA; EN	Ex: 25 (NR); NR NEx: 25 (NR); NR (M/F 22/28 for whole sample)	NR	(4) 4xPM	NR	NR	NR; NR	LV; ceph	Pre-Post Tx	NR
Bowman 2000	rNRS; pract; USA; EN	Ex1/2: 70 (22/48); 18.6 yrs NEx: 50 (22/28); 13.8 yrs	Cl I & II	Ex1: (2) 2xUPM Ex2: (4) 4xPM	NR	Ex1/2: 27.6 mos Nex: 24.6 mos	EA; NR	LV; ceph Esthetics; VAS	Pre-Post Tx	NR
Braga 2009	rNRS; Uni; BRA; PT	Ex: 15 (8/7); 13.2 yrs NEx: 15 (6/9); 13.0 yrs	C.I	(4) 2xU4/2xL4	NR	Ex: 57.6 mos NEx: 46.8 mos	NR; NR	LV; ceph	Pre-Post Tx	NR
Brant 2006	rNRS; Uni; BRA; PT	Ex: 15 (0/15); 12.8 yrs NEx: 15 (0/15); 11.8 yrs	Cl II/1	(4) 4xPM	NR	Ex: 41.0 mos NEx: 30.0 mos	HG	AV/LV; ceph	Pre-Post Tx	NR
Bravo 1997	uNRS; Uni; ESP; EN	Ex: 16 (0/16); 12.9 yrs NEx: 15 (0/15); 13.5 yrs	Cl.II; ALD	(4) 4xPM	NR	Ex: 32.4 mos Nex: 31.2 yrs	EA; NR, NR	AV/LV; ceph	Pre-Post Tx	NR
Carvalho 2000; Janson 2007a	rNRS; Uni; BRA; EN	Ex1: 27 (12/15); 14.1 yrs Ex2: 27 (12/15); 13.4 yrs	Cl II	Ex1: (3) asym. 3xPM Ex2: (4) sym. 4xPM	Ex1/2: HG, LB, elastics	Ex1: 31.7 mos Ex2: 28.8 mos	EA 0.022"; sliding mechanics	AV/LV; ceph	Pre-Post Tx	NR
Chang 2009	rNRS; hosp; KOR; EN	Adoles. Ex: 13 (0/13); 12.6 yrs Adult Ex: 19 (0/19); 22.4 yrs Adoles. NEx: 20 (0/20); 12.7 yrs Adult NEx: 16 (0/16); 22.9 yrs	NR	(4) 2xU4/2xL4	NR	Adoles. Ex: 33.6 mos Adult Ex: 28.3 mos Adoles. NEx: 25.2 mos Adult NEx: 25.8 mos	NR; NR	AV/LV; ceph	Pre/Post Tx	Funding; non-profit
Chung 2013	uNRS; Uni; KOR; KR	Ex: 59 (20/39); 18.4 yrs NEx: 60 (24/36); 18.9 yrs	NR	(2 or 4) PMs	NR	Ex: 32.0 mos NEx: 24.0 mos	NR	Esthetics; VAS	Post Tx	NR
Dai 2009	rNRS; Uni; CHN; CN	Ex1: 10 (NR); NR Ex2: 10 (NR); NR Ex3: 10 (NR); NR	Cl.I; high angle; bi-protr.	Ex1: (4) 2xU4/2xL4 Ex2/3: (4) 2xU4/2xL6	Ex1/2: NR Ex3: TADs	Ex1/2/3: 19.3 mos	MBT; sliding mechanics	AV/LV; ceph	Pre-Post Tx	NR
de Almeida-Pedrin 2009	rNRS; Uni; BRA; EN	Ex: 30 (15/15); 13.6 yrs NEx1: 22 (7/15); 13.8 yrs NEx2: 30 (15/15); 13.3 yrs	Cl.II	(2) 2xU4	Ex: Elastics/HG NEx1: Pendulum/HG NEx2: HG	Ex: 25.2 mos NEx1: 45.6 mos NEx2: 38.4 mos	NR; NR	AV/LV; ceph	Pre-Post Tx	None
Erdinc 2007	rNRS; Uni; USA; EN	Ex: 49 (19/30); 12.9 yrs NEx: 49 (19/30); 14.1 yrs	Cl.I & II/1	(4) 2xU4/2xL4	NR	Ex: 26.0 mos NEx: 21.0 mos	EA; NR	AV/LV; ceph	Pre-Post Tx/ +4.8 yrs	NR
Finnoy 1987	uNRS; Uni; NOR; EN	Ex: 30 (17/13); 11.7 yrs NEx: 30 (18/12); 11.4 yrs	Cl.II/1; OJ>4mm	(4) 4xPM	NR	Ex: 36.0 mos NEx: 39.6 mos	EA; NR	AV/LV; ceph	Pre-Post Tx/ +5.7 yrs	NR
Kinziger 2008; Frye 2008*	rNRS; Uni/pract; DEU; EN	Ex: 20 (NR); 17.6 yrs NEx: 20 (NR); 18.7 yrs	Cl. II/1	(4) 4xPM	Ex: TPA NEx: FFA	Ex: 46.0 mos NEx: 22.0 mos	NR; NR	AV/LV; ceph	Pre=Post Tx	NR
Germec 2008	RCT; Uni; TUR; EN	Ex: 13 (2/11); 18.1 yrs NEx: 13 (2/11); 17.8 yrs	BL Cl.I; ALD	(4) 4xPM	NEx: IPR	Ex: 24.8 mos NEx: 17.0 mos	Segmented mechs; coil springs; en masse	AV/LV; ceph	Pre-Post Tx	NR
Goeke 2009; Booij 2013	rNRS; pract/Uni; NLD/DEU; EN	Ex: 79 (41/38); 12.7 yrs NEx: 75 (40/35); 13.0 yrs	Cl.II/1; OJ≥4mm	(2) 2xU6	Ex: TPA, elastics NEx: FFA	Ex: 28.0 mos NEx: 20.0 mos	Ex: Begg technique NEx: FFA	AV/LV; ceph	Pre-Post Tx	None existing
Ismail 2002	pNRS; hosp; GBR; EN	Ex: 12 (NR); 14.4 yrs NEx: 12 (NR); 15.5 yrs	Cl.I	NR	NR	Ex: 23.6 mos NEx: 22.4 mos	PEA	AV/LV; ceph Front/lat. Phot.	Pre-Post Tx	NR
Itaborahy 2007	rNRS; pract; BRA; PT	Ex: 10 (8/2); 12.8 yrs NEx: 9 (6/3); 11.5 yrs	Cl.II/1	(4) 2xU4/2xL4	HG, elastics	Ex: 26.0 mos NEx: 24.0 mos	SEA; en masse	AV/LV; ceph	Pre-Post Tx	NR

Janson 2005	rNRS; Uni; BRA; PT	Ex1: 98 (31/67); 13.1 yrs Ex2: 43 (25/18); 12.9 yrs	Cl.II	Ex1: (2) 2xUPM Ex2: (4) 4xPM	NR	NR	EA; NR	AV/LV; ceph	Pre-Post Tx	NR
Janson 2007b	rNRS; Uni; BRA; EN	Ex: 22 (10/12); 12.9 yrs NEx: 22 (10/12); 12.5 yrs	Cl. II	(2) 2xU4	Ex: HG/TPA NEx: HG	Ex: 29.5 mos Nex: 31.4 mos	0.022”; en masse	AV/LV; ceph	Pre-Post Tx	NR
Junqueira 2012; Janson 2016	rNRS; Uni; BRA; EN	Ex1: 25 (NR); 31.0[¥] yrs Ex2: 18 (NR); 32.8[¥] yrs NEx: 20 (NR); 30.8[¥] yrs	Cl.II/1	Ex1: (2) 2xUPM Ex2: (4) 4xPM	Ex1/Ex2/NEx: HG (some also FFA or elastics)	0.022“ system,	0.022”; en masse	AV/LV; ceph Front/lat. Phot.	15.1 yrs post Tx	NR
Katsaros 1996	uNRS; Uni; DEU; DE	Ex: 20 (0/20); 13.0 yrs NEx: 20 (0/20); 12.1 yrs	OJ≥6mm	(4) 4xPM	NR	Ex: 44.4 mos NEx: 37.2 mos	NR; NR	AV/LV; ceph	Pre-Post Tx	NR
Khan 2010	rNRS; Uni; PAK; EN	Ex: 17 (4/13); 14.5 yrs NEx: 17 (4/13); 14.7 yrs	Cl.I & II	(4) 4xPM	NR	Ex: 31.0 mos NEx: 25.0 mos	NR; NR	AV/LV; ceph	Pre-Post Tx	NR
Kim 2007	rNRS; Uni; KOR; KR	Ex1: 20 (9/11); 14.6 yrs Ex2: 20 (8/12); 17.6 yrs	OJ>7mm	Ex1: (2) 2xUPM Ex2: (4) 4xPM	NR	Ex1: 22.8 mos Ex2: 25.2 mos	NR; NR	AV/LV; ceph	Pre-Post Tx	NR
Kinziger 2008[£]	uNRS; Uni; DEU; EN	Ex: 20 (NR); 17.6 yrs NEx: 20 (NR); 18.7 yrs	Cl II, d1	(2) 2xUPM	Ex: TPA NEx: FFA	NR, NR	NR; NR	AV/LV; ceph	Pre=Post Tx	NR
Kirschneck 2016	rNRS; Uni; DEU; EN	Ex: 25 (10/15); 10.8 yrs NEx: 25 (11/14), 11.1 yrs	$_{d/s}$Cl.I-II-III; OJ 5-9mm; ALD >6mm	(4) 4xPM	Ex/NEx: HG, elastics	Ex: 34.8 yrs NEx: 33.6 yrs[‡]	MBT 0.022”; sliding mechs$_{19x55}$	AV/LV; ceph	Pre-Post Tx	None
Kocadereli 2002	uNRS; Uni; TUR; EN	Ex: 40 (17/23); 12.8 yrs NEx: 40 (16/24); 12.3 yrs	Cl.I; ALD	(4) 2xU4/2xL4	NR	Ex: 31.5 mos NEx: 26.4 mos	EA; NR	AV/LV; ceph	Pre-Post Tx	NR
Konstantonis 2012	rNRS; Uni; USA; EN	Ex: 30 (NR); NR NEx: 32 (NR); NR	BL $_{d/s}$Cl. I	(4) 2xU4/2xL4	NR	NR	NR; NR	AV/LV; ceph	Pre-Post Tx	NR
Kumari 2010	rNRS; Uni; PAK; EN	Ex: 40 (NR); 15.4 yrs NEx: 41 (NR); 15.8 yrs	$_{s}$Cl.I	(4) 2xU4/2xL4	NR	NR	Roth 0.022”; NR	AV/LV; ceph	Pre-Post Tx	NR
Lim 2008	rNRS; Uni; KOR; EN	Ex: 50 (9/41); 18.9 yrs NEx: 50 (13/37); 18.2 yrs	BL Cl.I & II/1	(4) 4xPM	NR	Ex: 27.2 mos NEx: 23.0 mos	SEA; NR	LL/E-line; ceph Esthetics; VAS	Pre-Post Tx	NR
Lin 2004	rNRS; Uni; AUS; EN	Ex1: 22 (22/0); 13.5 yrs Ex2: 33 (33/0); 14.3 yrs Ex3: 12 (12/0); 14.3 yrs NEx: 30 (30/0); 11.9 yrs	Cl.I & II	Ex1: (4) 2xU4/2xL4 Ex2: (4) 2xU4/2xL5 Ex3: (4) 2xU5/2xL5	HG, elastics	Ex1: 27.0 mos Ex2: 28.0 mos Ex3: 25.0 mos NEx: 31.0 mos	0.018”; HG, NR	AV/LV; ceph	Pre-Post Tx	Funding; non-profit
Moraes 2001	rNRS; Uni; BRA; PT	Ex: 13 (0/13); 12.4 yrs NEx: 13 (0/13); 12.1 yrs	Cl.II/1	(4) 4xPM	NR	NR	NR	AV; ceph	Pre-Post Tx	NR
Moseling 2004	rNRS; Uni; AUS; EN	Ex1: 12 (0/12); 13.5 yrs Ex2: 24 (0/24); 12.9 yrs Ex3: 26 (0/26); 13.8 yrs NEx: 75 (0/75); 12.8 yrs	Cl.I & II; ALD	Ex1: (4) 2xU4/2xL4 Ex2: (4) 2xU4/2xL5 Ex3: (4) 2xU5/2xL5	HG, elastics	Ex1: 25.0 mos Ex2: 25.0 mos Ex3: 26.0 mos NEx: 26.0 mos	PEA 0.018’; NR	AV/LV; ceph	Pre-Post Tx	NR
Porto 2008	rNRS; Uni; BRA; PT	Ex: 23 (9/14); 12.3 yrs NEx: 23 (11/12); 12.4 yrs	Cl.II/1	(4) 2xU4/2xL4	Ex/NEx: HG	Ex: 29.8 mos NEx: 26.2 mos	NR	AV/LV; ceph	Pre-Post Tx	NR
Pudyani 2013	rNRS; Uni; IDN; ID	Ex: 13 (NR); NR NEx: 15 (NR); NR	BL Cl.I	(4) 2xU5/2xL5	NR	NR	PEA	AV/LV; ceph	Pre-Post Tx	NR
Sathekge 2005	rNRS; Uni; ZAF; EN	Ex: 14 (0/14); NEx: 4 (0/4);	NR	NR	NR	NR	NR	LV; ceph	Pre-Post Tx	NR
Sealens 1998	uNRS; Uni/pract; BEL; EN	Ex1: 30 (13/17); 11.8 yrs Ex2: 30 (19/11); 13.0 yrs NEx: 30 (12/18); 14.8 yrs	Cl.I-II-III	Ex1: (4) 2xU4/2xL4 Ex2: (4) 2xU5/2xL5	Elastics	Ex1: 34.0 mos Ex2: 30.0 mos NEx: 31.0 mos	Begg; NR	AV/LV; ceph	Pre-Post Tx	NR
Shirvani 2016	rNRS; Uni; IRN; EN	Ex1: 31 (NR); adult NEx: 31 (NR); adult	NR	(4) 2xU4/2xL4	NR	NR	NR; NR	AV/LV; ceph	Pre-Post Tx	None existing
Stephens 2005	rNRS; pract; USA; EN	Ex: 20 (6/14); NR NEx: 20 (6/14); NR	Cl.I & II	(4) 4xPM	NR	NR	NR; NR	AV/LV; ceph Esthetics; VAS	Post Tx/ +14.9 yrs	NR
Upadhyay 2010; 2012	pNRS; Uni; IND/USA; EN	Ex: 14 (0/14); 17.4 yrs NEx:18 (0/18); 16.5 yrs	Cl.II; OJ≥6mm; ALD≤3mm	(2) 2xU4	Ex:TADs NEx: FFA	Ex: 25.4 mos NEx: 21.6 mos	Roth 0.022”; sliding mechs en masse$_{17x25}$	AV/LV; ceph	Pre-Post A-P correction	NR
Verma 2013	rNRS; Uni; IND; EN	Ex: 50 (0/50); 14.1 yrs NEx: 50 (0/50); 13.4 yrs	Cl.I & BL Cl.II/1; ANB<5°	(4) 2xU4/2xL4	NR	Ex: 27.0 mos NEx: 21.0 mos	EA; NR	AV/LV; ceph	Pre-Post Tx	None
Weyrich 2009[$]	uNRS; Uni; DEU; EN	Ex1: 34 (NR); 13.1 yrs Ex2: 37 (NR); 11.3 yrs NEx: 32 (NR); 9.6 yrs	Cl.II/1	Ex1: (2) 2xUPM Ex2: (4) 4xPM	Ex4/NEx: RFA; elastics	Ex1: 38.6 mos Ex2: 41.9 mos NEx: 46.6 mos	NR; NR	LV; ceph	Pre-Post Tx	NR
Wholley 2003	rNRS; pract; AUS; EN	Ex1: 24 (NR); 13.4 yrs Ex2: 26 (NR); 13.5 yrs Ex3: 30 (NR); 13.8 yrs	NR	Ex1: (4) 2xU4/2xL4 Ex2: (4) 2xU5/2xL5 Ex3: (4) 2xU4/2xL5	Elastics	Ex1: 26.7 mos Ex2: 25.9 mos Ex3: 26.0 mos	PEA 0.018’’; NR	LV; ceph	Pre-Post Tx	NR
Xu 2004; 2006	rNRS; Uni; CHN; CN/EN	Ex1: 13 (4/9); 12.5 yrs Ex2: 8 (1/7); 12.5 yrs NEx: 12 (6/6); 12.1 yrs	BL Cl.I-II-III	Ex1: (4) 2xU4/2xL4 Ex2: (4) 2xU5/2xL5	NR	Ex1: 25.2 mos Ex2: 23.9 mos Nex: 22.1 mos	NR, NR	AV/LV; ceph	Pre-Post Tx	NR
Zafarmand 2015	rNRS; Uni; IRN; EN	Ex1: 30 (NR); Ex2: 30 (NR);	Cl.II/1	Ex1: (2) 2xU4 Ex2: (4) 2xU4/2xL4	NR	NR	EA; NR	LV; ceph	Pre-Post Tx	NR

Zhang 2009	rNRS; Uni; CHN; CN	Ex1: 25 (9/16); 12.2 yrs Ex2: 25 (9/16); 13.0 yrs	Cl.I	Ex1: (4) 2xU4/2xL4 Ex2: (4) 2xU5/2xL5	NR	Ex1: 29.8 mos Ex2: 26.4 mos	PEA; NR	AV/LV; ceph	Pre-Post Tx	NR
Zierhut 2000	uNRS, uni, USA, EN	Ex: 23 (11/12); 12.6 yrs NEx: 40 (19/21); 11.3 yrs	Cl.II/1; OJ≥5mm	(4) 2xU4/2xL4	HG	Ex: 34.8 mos NEx: 30.0 mos	EA; NR	AV/LV; ceph	Pre-Post Tx/ +13.8 yrs	NR
Zimmer 2016	rNRS, NR, NR, EN	Ex: 22 (10/12); 11.7 yrs NEx: 24 (10/14); 12.6 yrs	Cl.III	(2) 2xL5 or 2xL6	NR	Ex: 41.6 mos NEx: 33.1 mos	Roth 0.018”; NR	AV/LV; ceph	Pre-Post Tx	None

ALD, arch length discrepancy; Cl., Angle’s Class; DSR, digital subtraction radiography; EA, Edgewise appliance; Ex, extraction group; M/F, male/female; mo, month; NEx, non-extraction group; NR, not reported; pNRS, prospective non-randomized study; rNRS, retrospective non-randomized study; SS, stainless steel; TPA, transpalatal archwires; Tx, treatment; Uni, university; uNRS, unclear non-randomized study; yr, year.

[¥] Age at treatment’s end. Baseline age not reported.
[$]A retention period of one year was assumed and subtracted from the reported treatment duration to calculate active treatment time.
*Thesis and published paper with big similarities, but slight differences in the number of finally included patients in each group—the published paper was taken as reference and the thesis was used only to supplement an additional patient group; historical ‘normal’ growth sample reported in study omitted; one trial arm with patients treated with bilateral sagittal split osteotomy has been omitted.
[‡]The extraction and non-extraction groups were externally matched to treatment duration.
[†]Bishara included only good-treated patients!

Table S7. Risk of bias of the identified randomized clinical trial.

Trial	Sequence generation	Allocation concealment	Blinding of participants/ personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Germec 2008	**High risk** – quasi-randomization: "were randomly divided into 2 groups in the order of their referral to the orthodontic clinic: the first patient was assigned to the extraction group, and the next one to the nonextraction group"	**Unclear** - no information provided.	**Unclear** - Blinding is impractical for both patients and clinician; outcomes are objective, but no mention of outcome assessment blinding.	**High risk** - no mention of blinding throughout the paper; blinding could have been implemented.	**Low risk** - no drop-outs or patient losses are reported.	**Unclear** - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	**High risk** – no indication of baseline confounding and amount of incisor reported. However, the male/female composition oft he sample limits the generalizability of the trial's results.

Table S8. Risk of bias of the identified non-randomized clinical studies.

	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15	S16	S17	S18	S19	S20	S21	S22	S23	S24	S25	S26	S27	S28	S29	S30
Q1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q2	Y	Y/N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N
Q3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y/N	Y	Y	Y	Y	Y/N	Y	Y	N	Y/N	Y/N	Y	Y/N	Y	Y/N	Y	Y	Y/N	Y	Y
Q4	N	Y	Y/N	Y/N	Y	Y/N	Y/N	Y	Y/N	Y	N	Y	Y	N	N	N	Y	Y/N	N	N	N	Y	N	Y	N	Y	N	Y	Y/N	Y
Q5	Y/N	Y	Y/N	N	Y/N	Y	Y/N	Y	Y/N	Y/N	Y/N	Y/N	Y	Y	Y/N	Y/N	Y	Y/N	N	Y/N	N	Y	Y/N	Y	N	Y/N	N	Y	Y/N	Y
Q6	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y/N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q7	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y/N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q8	Y	Y	N	Y	Y	N	N	N	N	Y	N	Y	Y	N	Y	Y	N	N	N	Y	Y	Y	Y	N	Y	Y	N	N	Y	Y
Q9	UTD	N	UTD	UTD	N	N	N	Y	Y	Y	UTD	UTD	Y	N	UTD	N	Y	UTD	UTD	N	N	Y	UTD	Y	N	N	N	UTD	UTD	N
Q10	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	Y	N	N	N	N
Q11	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	Y	N	N	N	N	N	N	Y/N	N	Y
Q12	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N
Q13	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y/N	Y	Y	Y	Y	Y	UTD	Y/N	Y	Y	Y	Y	Y	Y	Y/N	Y
Q14	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q15	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q16	Y	Y/N	Y	Y	Y	UTD	Y	Y	Y	N	Y	Y	Y	UTD	Y	UTD	UTD	UTD	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y
Q17	Y/N	Y/N	Y/N	Y/N	Y/N	UTD	UTD	UTD	UTD	UTD	UTD	UTD	UTD	UTD	Y	UTD	Y	UTD	UTD	UTD	UTD	UTD	Y	UTD	UTD	Y	UTD	UTD	UTD	UTD
Q18	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Q19	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Q20	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	Y	N	N	N	N	N	N	N	N	N	N	N
Q21	3	3	4	0	0	0	2	2	2	5	0	0	1	1	0	1	1	3	2	4	0	1	0	2	2	0	4	2	0	2

Studies

S1-Basciftci 2003; S2-Bishara 1994; S3-Bowman 2000; S4-Braga 2009; S5-Brant 2006; S6-Bravo 1997; S7-Chang 2009; S8-de Almeida 2009; S9-Finnoy 1987; S10-Goeke 2009; S11-Ismail 2002; S12-Itaborahy 2007; S13-Janson 2007; S14-Katsaros 1996; S15-Khan 2010; S16-Frye 2008; S17-Kirschneck 2016; S18-Kocadereli 2002; S19-Konstantonis 2012; S20-Lim 2008; S21-Moraes 2001; S22-Porto 2008; S23-Pudyani 2013;S24-Saelens 1998; S25-Shirvani 2016; S26-Upadhyay 2010; S27-Verma 2013; S28-Weyrich 2009/Berg 2008; S29-Xu 2004; S30-Zierhut 2000.

Y, yes; Y/N, partly yes/no; N, no; UTD, unable to determine.

Table S9. Results of the Bowman and Johnston 2000 study – patient demographics.

	NonEx	**Ex**
Patients	50	70
Male - n (%)	22 (44%)	22 (31%)
Female - n (%)	28 (56%)	48 (69%)
Age - mean (SD)	13.82 (4.99)	18.69 (10.04)
Lower lip – E plane - mean (SD)	-0.16 (2.67)	-0.19 (2.94)
Class I	22 (44%)	34 (49%)
Class II	23 (46%)	31 (44%)
Class II subdiv	5 (10%)	5 (7%)
Treatment duration - mean (SD)	24.98 (5.25)	27.61 (4.50)

SD, standard deviation; Ex, extraction; NonEx, non-extraction.

Table S10. Results of the Bowman and Johnston 2000 study – crude and adjusted linear regression analyses of Ex (2 or 4 premolars) and Non-Ex groups.

			Univariable			Multivariable	
Outcome	**Factor**	**Category**	**b (95% CI)**	**P**		**b (95% CI)**	**P**
Change in LL-EL	Extraction	Non-Ex	Referent			Referent	
		2/4xPM	-1.84 (-2.53,-1.15)	<0.001*		-1.87 (-2.55,-1.18)	<0.001*
	Sex	Female	Referent			Referent	
		Male		0.05		-0.76 (-1.46,-0.06)	0.03*
	Age	Per year		0.72		NT	
	Class	Cl. I	Referent	0.10		Referent	
		Cl. II/1-2				0.37 (-0.33,1.08)	0.29
		Cl. II subdivision				0.43 (-0.82,1.67)	0.50
	Duration	Per month		0.07		-0.02 (-0.09,0.05)	0.55
	LL-EL T1	Per mm		<0.001*		-0.19 (-0.31,-0.07)	0.002*
VAS$_{0-100}$ (dentists)	Extraction	Non-Ex	Referent			Referent	
		2/4xPM	8.24 (4.06,12.41)	<0.001*		8.26 (4.21,12.32)	<0.001*
	Sex	Female	Referent			NT	
		Male		0.77			
	Age	Per year		0.44		NT	
	Class	Cl. I	Referent	0.68		NT	
		Cl. II/1-2					
		Cl. II subdivision					
	Duration	Per month		0.79		NT	
	LL-EL T1	Per mm		0.008*		1.03 (0.32,1.74)	0.005*
VAS$_{0-100}$ (laypersons)	Extraction	Non-Ex	Referent			Referent	
		2/4xPM	2.94 (-1.41,7.29)	0.18		2.97 (-1.25,7.19)	0.17
	Sex	Female	Referent			NT	
		Male		0.95			
	Age	Per year		0.54		NT	
	Class	Cl. I	Referent	0.47		NT	
		Cl. II/1-2					
		Cl. II subdivision					
	Duration	Per month		0.34		NT	
	LL-EL T1	Per mm		0.005*		1.08 (0.33,1.82)	0.005*
VAS$_{0-100}$ (combined)	Extraction	Non-Ex	Referent			Referent	
		2/4xPM	4.15 (0.07,8.23)	0.05*		4.43 (0.46,8.40)	0.03*
	Sex	Female	Referent	0.60		NT	
		Male					
	Age	Per year		0.64		NT	
	Class	Cl. I	Referent	0.11		Referent	
		Cl. II/1-2				1.90 (-2.18,5.98)	0.36
		Cl. II subdivision				7.73 (0.33,15.13)	0.04*
	Duration	Per month		0.53		NT	
	LL-EL T1	Per mm		0.02*		0.92 (0.22,1.62)	0.01*
Treatment duration	Extraction	Non-Ex	Referent			Referent	
		2/4xPM	2.63 (0.86,4.40)	0.004*		2.75 (1.02,4.48)	0.002*
	Sex	Female	Referent			NT	
		Male		0.84			
	Age	Per year		0.69		NT	
	Class	Cl. I	Referent	0.02*		Referent	
		Cl. II/1-2				2.45 (0.67,4.23)	0.007*
		Cl. II subdivision				2.53 (-0.68,5.73)	0.12
	LL-EL T1	Per mm		0.38		NT	

b, unstandardized regression coefficient; CI, confidence interval; Ex, extraction; LL-EL, lower lip to E plane; Non-Ex, non-extraction; NT, not tested; PM, premolar; VAS$_{0-100}$, visual analogue scale from 0 to 100 (higher score indicate more pleasant profile).

Table S11. Results of the Bowman and Johnston 2000 study – crude and adjusted linear regression analyses of Ex (2 premolars), Ex (4 premolars), and Non-Ex groups

			Univariable			**Multivariable**	
Outcome	**Factor**	**Category**	**b (95% CI)**	**P**		**b (95% CI)**	**P**
Change in LL-EL	Extraction	Non-Ex	Referent			Referent	
		2xPM	-0.83 (-1.84,0.17)	0.10		-1.12 (-2.15,-0.08)	0.03*
		4xPM	-2.19 (-2.91,-1.47)	<0.001*		-2.13 (-2.86,-1.40)	<0.001*
	Sex	Female	Referent			Referent	
		Male		0.05*		-0.72 (-1.41,-0.03)	0.04*
	Age	Per year		0.72		NT	
	Class	Cl. I	Referent	0.10		Referent	
		Cl. II/1-2				0.09 (-0.67,0.85)	0.82
		Cl. II subdivision				0.34 (-0.89,1.58)	0.58
	Duration	Per month		0.07		-0.02 (-0.09,0.05)	0.55
	LL-EL T1	Per mm		0.001*		-0.17 (-0.29,-0.06)	0.004*
VAS_{0-100} (dentists)	Extraction	Non-Ex	Referent			Referent	
		2xPM	9.30 (3.07,15.52)	0.004*		10.14 (4.09,16.19)	0.001*
		4xPM	7.87 (3.38,12.35)	0.001*		7.62 (3.27,11.96)	0.001*
	Sex	Female	Referent			NT	
		Male		0.77			
	Age	Per year		0.44		NT	
	Class	Cl. I	Referent	0.68		NT	
		Cl. II/1-2					
		Cl. II subdivision					
	Duration	Per month		0.79		NT	
	LL-EL T1	Per mm		0.008*		1.07 (0.35,1.79)	0.004*
VAS_{0-100} (laypersons)	Extraction	Non-Ex	Referent			Referent	
		2xPM	5.92 (-0.52,12.36)	0.07		6.83 (0.58,13.08)	0.03*
		4xPM	1.91 (-2.74,6.55)	0.42		1.64 (-2.85,6.12)	0.47
	Sex	Female	Referent	0.95		NT	
		Male					
	Age	Per year		0.54		NT	
	Class	Cl. I	Referent	0.47		NT	
		Cl. II/1-2					
		Cl. II subdivision					
	Duration	Per month		0.34		NT	
	LL-EL T1	Per mm		0.005*		1.15 (0.41,1.89)	0.003*
VAS_{0-100} (combined)	Extraction	Non-Ex	Referent			Referent	
		2xPM	6.25 (0.20,12.31)	0.04*		6.96 (0.76,13.17)	0.03*
		4xPM	3.42 (-0.94,7.79)	0.12		3.52 (-0.80,7.84)	7.84
	Sex	Female	Referent	0.60		NT	
		Male					
	Age	Per year		0.64		NT	
	Class	Cl. I	Referent	0.11		Referent	
		Cl. II/1-2				0.90 (-3.59,5.39)	0.69
		Cl. II subdivision				7.42 (0.00,14.84)	0.05*
	Duration	Per month		0.53		NT	
	LL-EL T1	Per mm		0.02*		0.97 (0.26,1.68)	0.008*
Treatment duration	Extraction	Non-Ex	Referent			Referent	
		2xPM	3.46 (0.83,6.09)	0.01*		2.48 (-0.21,5.18)	0.07
		4xPM	2.35 (0.45,4.24)	0.02*		2.84 (0.96,4.73)	0.003*
	Sex	Female	Referent	0.84		NT	
		Male					
	Age	Per year		0.69		NT	
	Class	Cl. I	Referent	0.02		Referent	
		Cl. II/1-2				2.56 (0.60,4.52)	0.01*
		Cl. II subdivision				2.57 (-0.67,5.80)	0.12
	LL-EL T1	Per mm		0.38		NT	

b, unstandardized regression coefficient; CI, confidence interval; Ex, extraction; LL-EL, lower lip to E plane; Non-Ex, non-extraction; NT, not tested; PM, premolar; VAS_{0-100}, visual analogue scale from 0 to 100 (higher score indicate more pleasant profile).

Table S12. Initial meta-analyses done on studies with pooled trial arms.

Outcome	**Studies (patients)**	**MD**	**95% CI**	**P**		**I^2 (95% CI)**	**tau^2 (95% CI)**		**95% PrI**
LL-EL	24 (1456)	-1.96	-2.49,-1.44	<0.001		86% (76%,93%)	1.44 (0.74,3.16)		-4.51,0.59
UL-EL	21 (1149)	-1.26	-1.81,-0.71	<0.001		85% (74%,93%)	1.32 (0.68,3.09)		-3.74,1.22
NLA	21 (1089)	4.21	2.98,5.45	<0.001		49% (25%,73%)	3.49 (1.20,10.12)		0.08,8.34
SPC	6 (408)	1.24	0.05,2.44	0.04		66% (19%,94%)	1.33 (0.17,11.49)		-2.39,4.87

CI, confidence interval; LL-EL, lower lip to E plane; MD, mean difference; NLA, nasolabial angle; SPC, soft tissue profile convexity excluding the nose; PrI, predictive interval; UL-EL, upper lip to E plane.

Table S13. Subgroup analyses performed.

	LL-EL difference				UL-EL difference				NLA difference				SPC difference			
SG	**n**	**MD**	**95% CI**	**P_{SG}**	**n**	**MD**	**95% CI**	**P_{SG}**	**n**	**MD**	**95% CI**	**P_{SG}**	**n**	**MD**	**95% CI**	**P_{SG}**
4 x PM1	3	-2.00	-2.59,-1.41	0.32	3	-0.85	-1.49,-0.21	0.28	3	3.06	-0.78,6.91	0.33	2	0.28	-1.01,1.57	**0.01***
4 x PM2	10	-2.54	-3.20,-1.88		10	-1.61	-2.49,-0.74		10	4.95	2.81,7.09		4	2.66	1.88,3.43	
TAD	1	-4.58	-5.99,-3.17	0.16	1	-1.22	-2.10,-0.34	0.89	1	3.36	-1.66,8.38	0.85	NE			
No TAD	23	-1.87	-2.37,-1.36		20	-1.26	-1.84,-0.68		20	4.25	2.97,5.53					

CI, confidence interval; LL-EL, lower lip to E plane; MD, mean difference; NE, not estimable; NEx, non-extraction; NLA, nasolabial angle; SPC, profile soft tissue convexity excluding the nose; PM, premolar; PSG, P value for difference between subgroups; UL-EL, upper lip to E plane.
*statistically significant.

Fig. S1. Meta-regression of incisor retraction difference between Ex/Non-Ex groups (SMD) and treatment results.

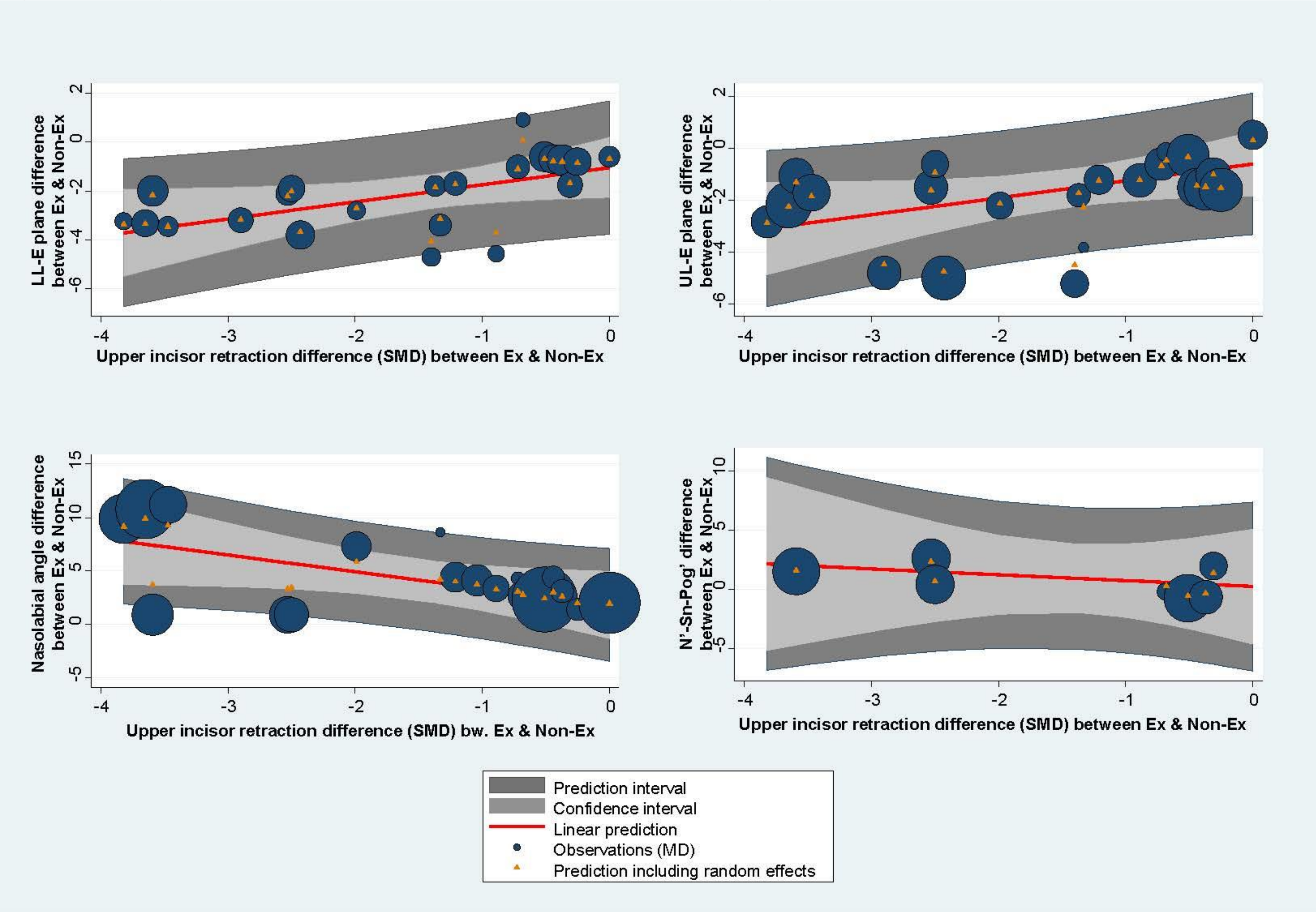

Table S14. Sensitivity analyses according to study design characteristics and Egger's test for reporting biases.

	LL-EL difference				**UL-EL difference**				**NLA difference**				**SPC difference**			
	n	**b**	**95% CI**	**P**	**n**	**b**	**95% CI**	**P**	**n**	**b**	**95% CI**	**P**	**n**	**b**	**95% CI**	**P**
'Borderline' stated in paper	28	-0.47	-1.68,0.74	0.43	24	0.15	-1.15,1.45	0.82	24	0.43	-2.48,3.34	0.76	8	1.30	-1.66,4.27	0.32
	n	**b**	**95% CI**	**P**	**n**	**b**	**95% CI**	**P**	**n**	**b**	**95% CI**	**P**	**n**	**b**	**95% CI**	**P**
Baseline Ex/Non-Ex imbalance of outcome (SMD)	27	-1.65	-2.62,-0.67	**0.002***	23	-1.34	-2.43,-0.25	**0.02***	23	-0.82	-5.42,3.78	0.72	8	0.18	-3.13,3.48	0.90
	n	**b**	**95% CI**	**P**	**n**	**b**	**95% CI**	**P**	**n**	**b**	**95% CI**	**P**	**n**	**b**	**95% CI**	**P**
Prospective study nature	28	-1.25	-3.20,0.71	0.20	24	-0.08	-2.03,1.87	0.93	24	0.05	-4.65,4.74	0.98	8	NE		
	n	**b**	**95% CI**	**P**	**n**	**b**	**95% CI**	**P**	**n**	**b**	**95% CI**	**P**	**n**	**b**	**95% CI**	**P**
Egger's test	28	-1.57	-5.31,2.16	0.39	24	2.03	-2.15,6.20	0.33	24	0.08	-1.73,1.88	0.93	8	-1.68	-5.92,2.55	0.37

b, meta-regresssion coefficient; CI, confidence interval; Ex, extraction group; LL-EL, lower lip to E plane; MD, mean difference; NE, not estimable; NEx, non-extraction group; NLA, nasolabial angle; SPC, profile soft tissue convexity excluding the nose; SMD, standardized mean difference; UL-EL, upper lip to E plane.
*statistically significant.

Fig. S2. Graph indicating baseline comparability of synthesized studies for the outcome of lower lip to E plane using the Standardized Mean Difference (SMD) to assess baseline differences. Studies depicted red were omitted from the sensitivity analysis.

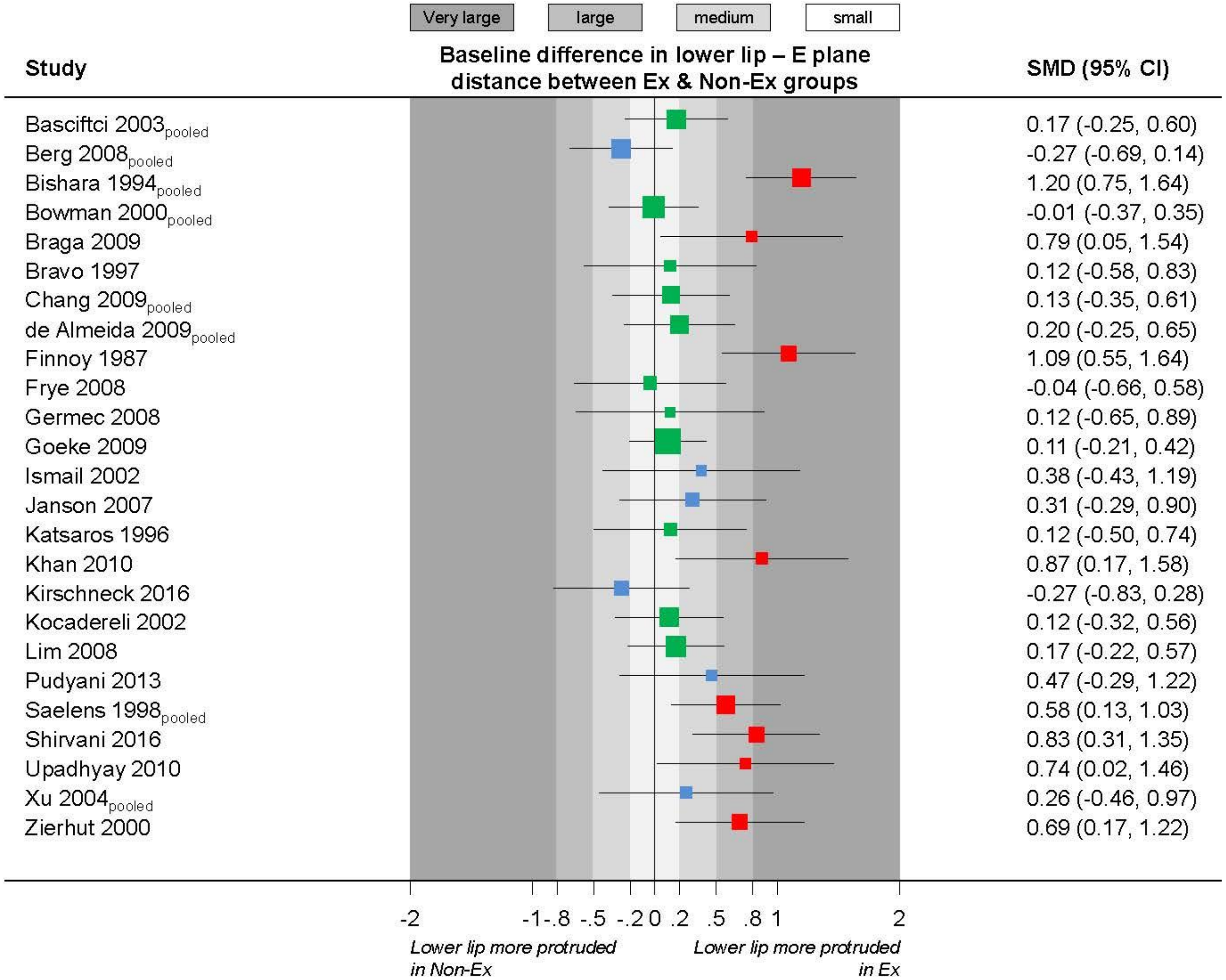

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Fig. S3. Graph indicating baseline comparability of synthesized studies for the outcome of upper lip to E plane using the Standardized Mean Difference (SMD) to assess baseline differences. Studies depicted red were omitted from the sensitivity analysis.

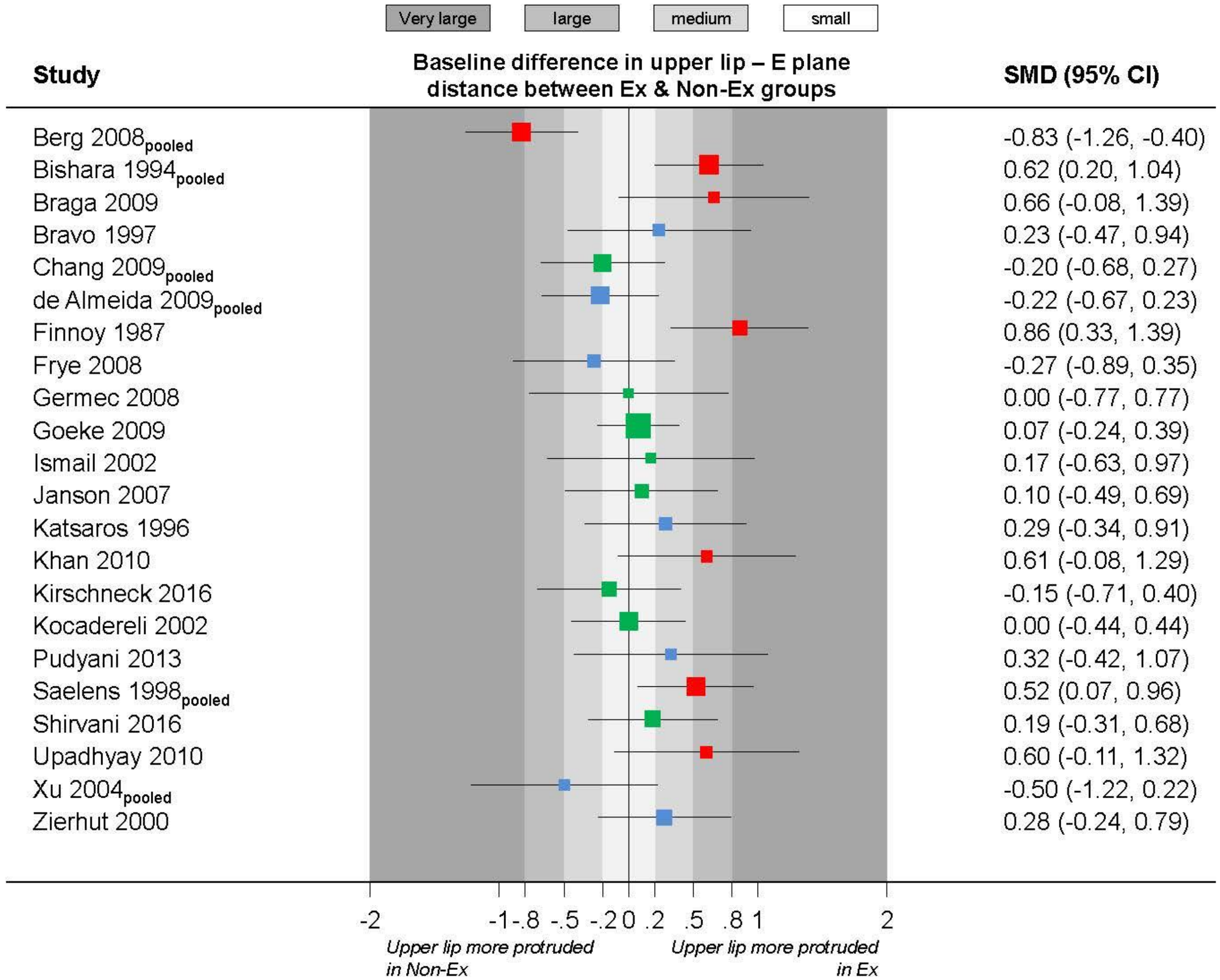

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Fig. S4. Graph indicating baseline comparability of synthesized studies for the outcome of nasolabial angle using the Standardized Mean Difference (SMD) to assess baseline differences. Studies depicted red were omitted from the sensitivity analysis.

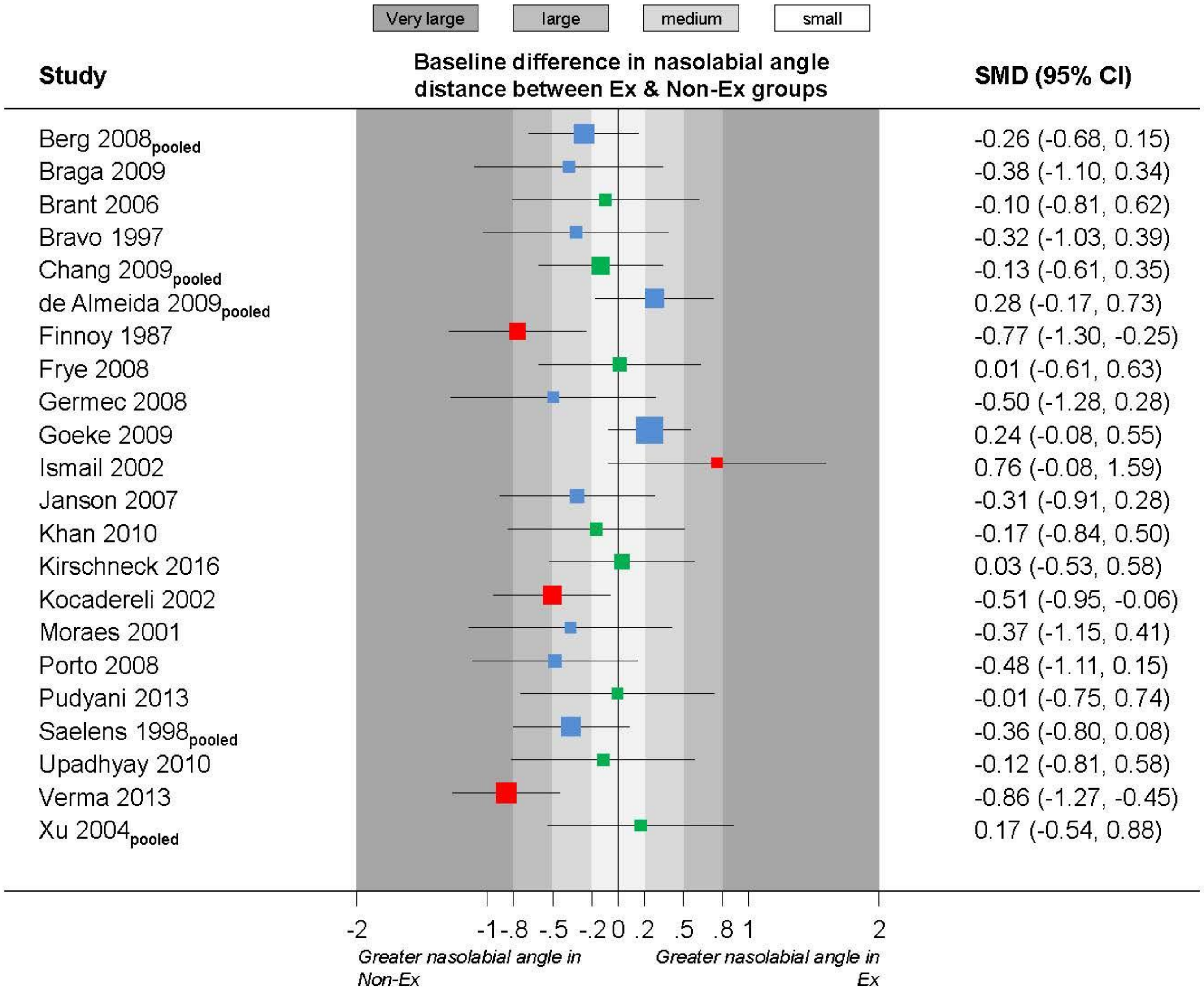

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Fig. S5. Graph indicating baseline comparability of synthesized studies for the outcome of soft tissue profile convexity using the Standardized Mean Difference (SMD) to assess baseline differences. Studies depicted red were omitted from the sensitivity analysis.

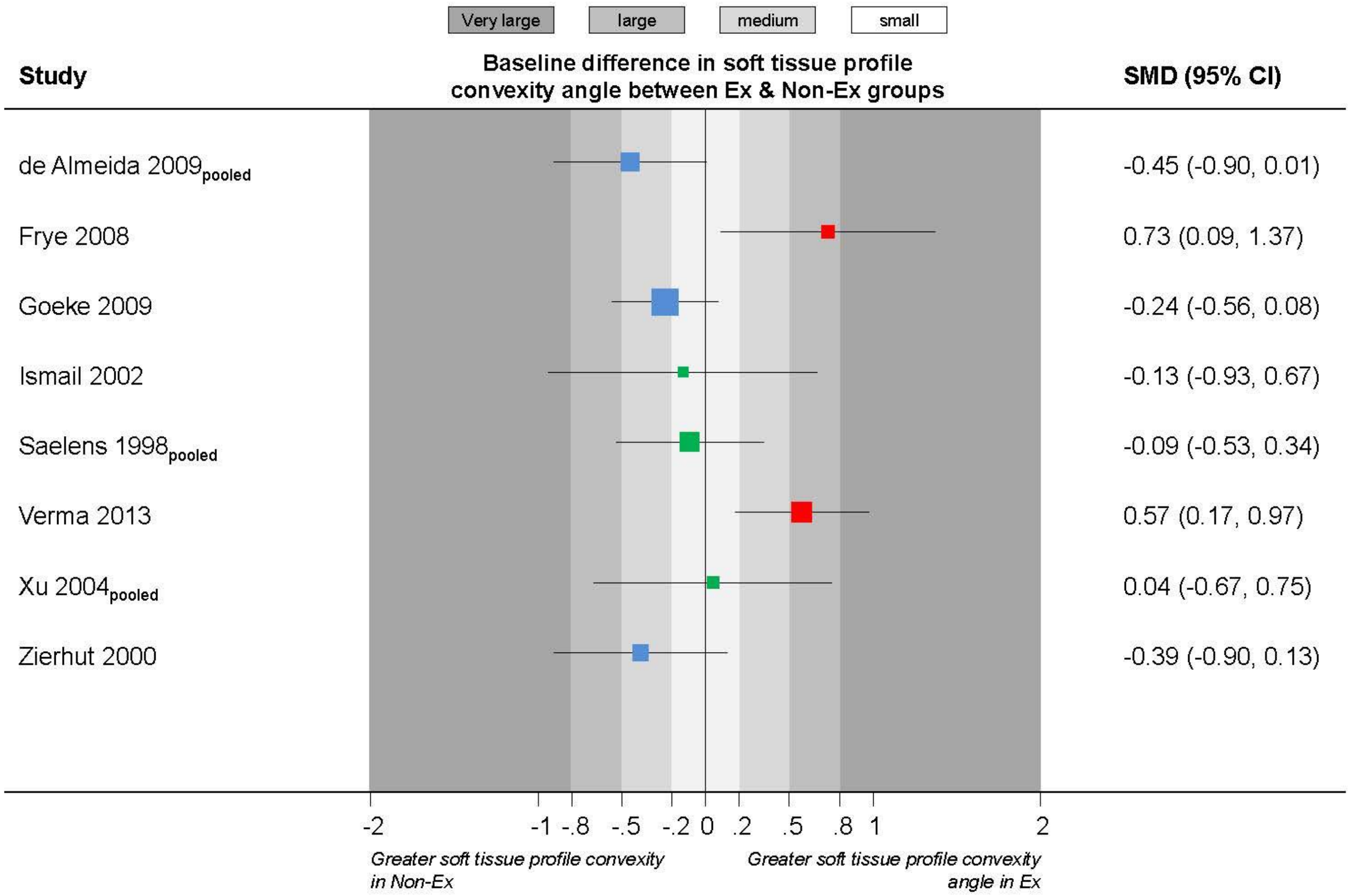

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Fig S6. Graph indicating baseline comparability of synthesized studies for the covariate of upper incisor sagittal position using the Standardized Mean Difference (SMD) to assess baseline differences. Studies depicted red were omitted from the sensitivity analysis.

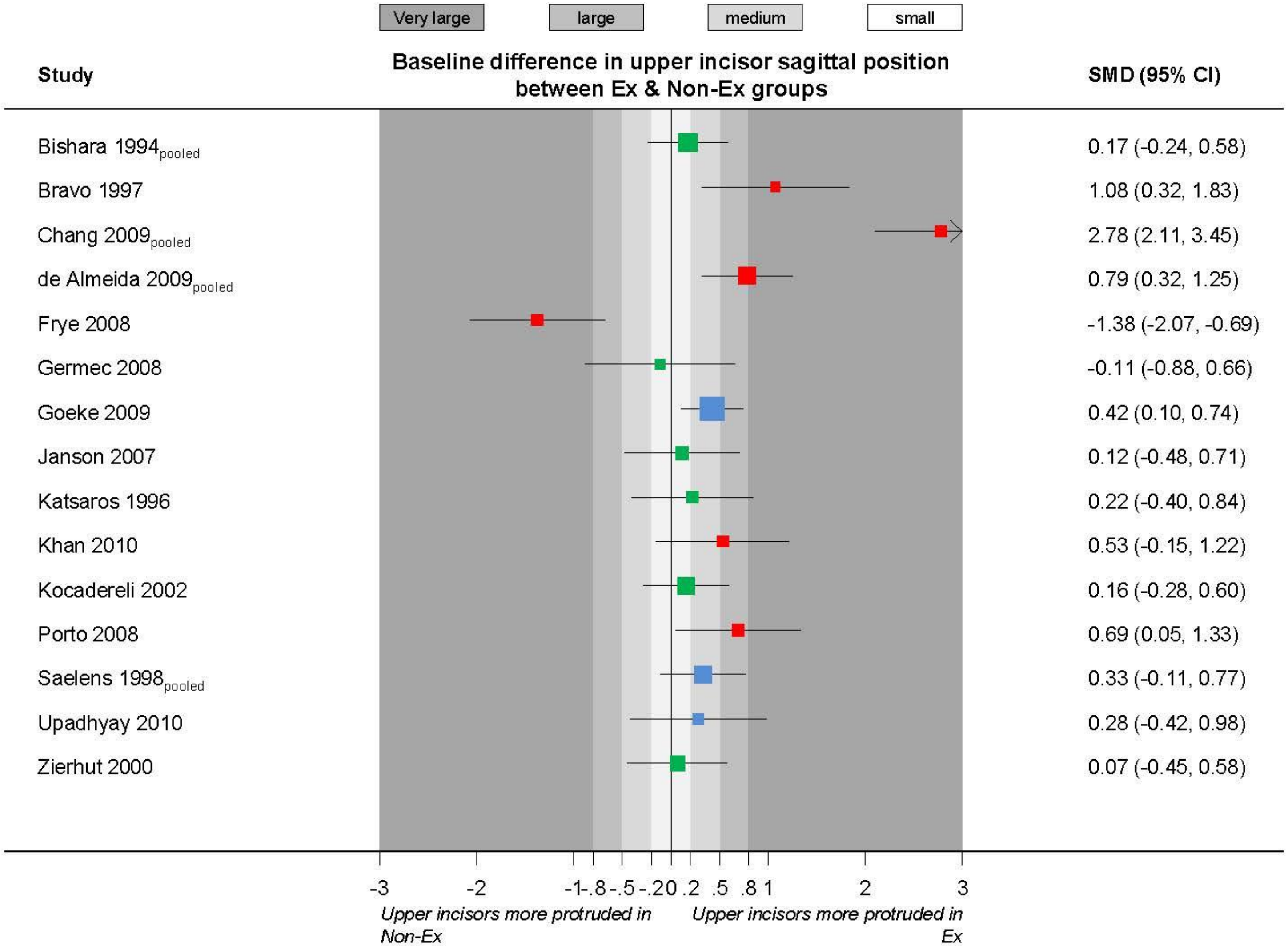

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Table S15. Details for the GRADE assessment of Table 5.

Outcome	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large Effect	Dose Response	Residual Confounding
LL-EL 2 PM Ex	Starts from "low", due to the inclusion of non-randomized studies. Downgraded further by one point due to serious limitations (high risk of bias).	Low heterogeneity; no reason to downgrade	Directly relevant	Adequate sample	Safe	Small to moderate effect magnitude; no reason to rate up	Evidence of dose-response relationship with amount of upper incisor retraction; however, risk of bias is high, which diminishes the credibility of this association.	Cannot be ruled out.
LL-EL 4 PM Ex	Same as LL-EL (2 PM Ex)	High heterogeneity, which might affect our confidence regarding Ex decision (studies on both sides of the forest plot); subgroup analyses explain part of the heterogeneity; downgrade by one.	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Cannot be ruled out.
UL-EL 2 PM Ex	Same as LL-EL (2 PM Ex)	Same as LL-EL (4 PM Ex)	Same as LL-EL (2 PM Ex)	Inadequate sample; the 95% CI includes both the null effect and large effect values, which indicates imprecision.	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Cannot be ruled out.
UL-EL 4 PM Ex	Same as LL-EL (2 PM Ex)	Moderate heterogeneity, which might affect our confidence regarding Ex decision (studies on both sides of the forest plot); subgroup analyses explain part of the heterogeneity; no robust reason to downgrade.	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Cannot be ruled out.
NLA 2 PM Ex	Same as LL-EL (2 PM Ex)	Low heterogeneity; no reason to downgrade	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Cannot be ruled out.
NLA 4 PM Ex	Same as LL-EL (2 PM Ex)	Same as UL-EL (4 PM Ex)	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Cannot be ruled out.
SPC 2 PM Ex	Same as LL-EL (2 PM Ex)	Low heterogeneity; no reason to downgrade	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	No dose response relation assessment.	Cannot be ruled out.
SPC 4 PM Ex	Same as LL-EL (2 PM Ex)	Low heterogeneity; no reason to downgrade	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Safe	Same as LL-EL (2 PM Ex)	Same as SPC (2 PM Ex)	Cannot be ruled out.
VAS 2/4 PM Ex	Same as LL-EL (2 PM Ex)	Low heterogeneity; no reason to downgrade	Same as LL-EL (2 PM Ex)	Same as LL-EL (2 PM Ex)	Safe	Same as LL-EL (2 PM Ex)	Same as SPC (2 PM Ex)	Cannot be ruled out.

Ex, extraction; LL-EL, lower lip to E plane; NLA, nasolabial angle; Non-Ex, non-extraction; PM, premolar; SPC, soft tissue profile convexity; UL-EL, upper lip to E plane.

Supplement 2. Supplementary Information on the review

Author contributions

DK conceived the idea. SNP wrote the first draft of the protocol. DD, DK, SNP, TE revised the protocol. SNP performed the literature searches and extracted search hits. DD and DK did screening by title, study selection by abstract and full-text, data extraction, and assessment of the risk of bias in duplicate, while SNP resolved any conflicts that arose. SNP handled communications with trialists, performed the statistical analysis, and wrote the first draft of the manuscript. DD, DK, SNP, TE assisted in the interpretation of the results and revised the manuscript draft. SNP submitted the manuscript, is the guarantor, and responsible for the accuracy of the data and for future updates of the review.

Data sharing

The full dataset from this study has been uploaded and is freely available through Zenodo. The individual patient data provided by Dr. Bowman have not been uploaded and can be requested by Dr. Bowman himself.

***Post hoc* changes to the protocol**

- A novel Paule Mandel estimator had been published after initial protocol writing. Since it has been reported to outperform the standard DerSimonian and Laird estimator for random-effects variance this was preferred for all analyses.
- Several subgroup analyses were planned in the PROSPERO protocol, but could not be performed due to limited data/incomplete reporting of the covariates: patient race, initial malocclusion, Discrepancy Index, appliances/mechanics used in treatment, one or two phase treatment.
- A subgroup analysis using treatment duration as covariate was planned in the protocol. However, during the review the review team concluded that this covariate has no direct clinical association with the treatment effects on profile, which diminishes the credibility of the subgroup analysis. We therefore omitted this subgroup analysis altogether.
- A vast number of outcomes were finally identified after study selection. In order to keep the risk of false positives due to multiple testing low, we limited our analyses to only a choice of outcome that bore a direct clinical relevance to both orthodontist and patient.

- Robustness of the results was a priori planned to be checked through sensitivity analyses by (i) inclusion of low risk of bias studies, (ii) inclusion of most precise studies in case of a significant Egger's test, and (iii) improvement of GRADE. However, all three sensitivity analyses could not be performes, as (iii) the vast majority of studies were in high risk of bias, (ii) Egger's test was not significant, and (iii) the reasons for GRADE downgrading were risk of bias, imprecision, and inconsistency. However, during the review procedures it became evident that most included studies are retrospective cohort studies with high risk of confounding. Therefore the baseline similarities of the Ex and Non-Ex groups were compared directly, and this baseline similarity (or lack thereof) were used to conduct a sensitivity analysis adjusting indirectly for baseline confounding by including only trials with baseline SMD ≤ 0.5 (moderate effect).